BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 May 2002 (30.05.2002)

PCT

(10) International Publication Number
WO 02/42304 A2

(51) International Patent Classification[7]: C07D 487/00

(21) International Application Number: PCT/US01/45792

(22) International Filing Date:
1 November 2001 (01.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/245,591	3 November 2000 (03.11.2000)	US
60/245,593	3 November 2000 (03.11.2000)	US
60/245,843	3 November 2000 (03.11.2000)	US
60/245,915	3 November 2000 (03.11.2000)	US
60/245,954	3 November 2000 (03.11.2000)	US

(71) Applicant: **WYETH** [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: **SABB, Annmarie, Louise**; 15 Meadow Lane, Pennington, NJ 08534 (US). **VOGEL, Robert, Lewis**; 20 Sleepy Hollow Road, Stratford, NJ 08084 (US). **NELSON, James, Albert**; 7 Decision Way West, Washington Crossing, PA 18977 (US). **ROSENZWEIG-LIPSON, Sharon, Joy**; 25 Bosko Drive, East Brunswick, NJ 08816 (US). **WELMAKER, Gregory, Scott**; 2 Jason Court, Jackson, NJ 08527 (US). **SABALSKI, Joan, Eileen**; 38 Elton Street, Yardville, NJ 08620 (US). **SMITH, Michael, David**; 315 Vista Way, Martinez, CA 94553 (US). **CHAN, Anita, Wai-Yin**; 1600 Center Avenue, Apartment 6D, Fort Lee, NJ 07024 (US). **ANTANE, Madelene, Miyoko**; 56 Lillie Street, West Windsor, NJ 08550 (US). **RAVEENDRANATH, Panolil**; 2 Whitman Place, Monroe, NY 10950 (US). **MEGATI, Sreenivasulu**; 1 Hearth Court, New City, NY 10956 (US).

(74) Agents: **ECK, Steven, R.**; WYETH, Patent Law Department, Five Giralda Farms, Madison, NJ 07940-0874 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

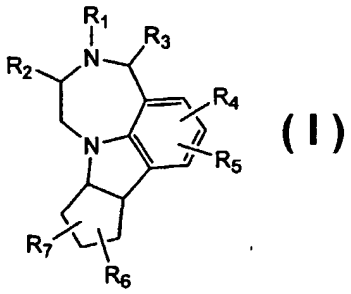
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

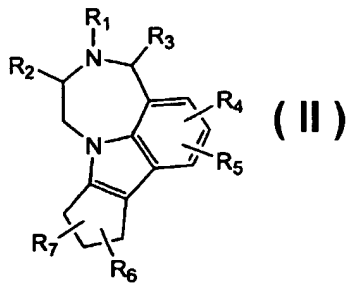
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

[Continued on next page]

(54) Title: CYCLOPENTA[b]1,4]DIAZEPINO[6,7,1-hi]INDOLES AND DERIVATIVES



(I)



(II)

(57) Abstract: This invention provides compounds of the formulae: (I) or (II), wherein: R_1 is hydrogen, alkyl of 1-6 carbon atoms, atoms, acyl of 2-7 carbon atoms, aryl, heteroaryl, or -C(O)R' wherein R' is alkyl of from 1 to 6 carbon atoms, aryl, or heteoaryl; R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, alkoxy of 1-6 carbon atoms, $-CH_2OH$, fluoroalkyl, alkyl sulfonamide of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluoroalkyl, -CN, alkyl sulfonamide of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluoroalkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, or aroyl; R_6 and R_7 are each independently hydrogen, C_1-C_6 alkyl or cycloalkyl; or a pharmaceutically acceptable salt thereof, as well as pharmaceutical compositions containing these compounds and methods for their use, including treatment of obsessive-compulsive disorder, panic disorder, depression, anxiety, generalized anxiety disorder, schizophrenia, migraine, sleep disorders, eating disorders, obesity, epilepsy, and spinal cord injury.

WO 02/42304 A2

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

CYCLOPENTA[b]1,4]DIAZEPINO[6,7,1-hi]INDOLES AND DERIVATIVES

The present invention relates to cyclopenta[b][1,4]diazepino[6,7,1-*hi*]indoles and derivatives thereof, processes for preparing them, pharmaceutical compositions containing them and intermediates used in their preparation. The active compounds of this invention are serotonin 5-hydroxytryptamine 2_C ($5HT_{2C}$) receptor agonists useful for the treatment of central nervous system disorders including, but not limited to, obsessive-compulsive disorder, depression, anxiety, generalized anxiety disorder, schizophrenia, panic disorder, migraine, sleep disorders, such as sleep apnea, eating disorders, such as hyperphagia, obesity, epilepsy, and spinal cord injury.

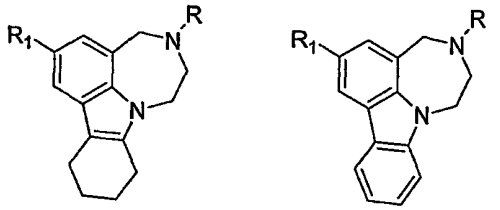
BACKGROUND OF THE INVENTION

Obesity is a medical disorder characterized by an excess of body fat or adipose tissue. Comorbidities associated with obesity are Type II diabetes, cardiovascular disease, hypertension, hyperlipidemia, stroke, osteoarthritis, sleep apnea, gall bladder disease, gout, some cancers, some infertility, and early mortality. As the percentage of obese individuals continues to rise both in the U.S. and abroad, obesity is expected to be a major health risk in the 21st Century. The serotonin 5-hydroxytryptamine (5-HT) receptor is a G-protein coupled receptor which is expressed in neurons in many regions of the human central nervous system. [Wilkinson, L. O. and Dourish, C. T. in *Serotonin Receptor Subtypes: Basic and Clinical Aspects* (ed. Peroutka, S. J.) 147-210 (Wiley-Liss, New York, 1991).] The $5HT_{2c}$ receptor (formerly called the $5HT_{1C}$ receptor) is a prominent subtype of the serotonin receptor found in the central nervous system of both rats and humans. It is expressed widely in both cortical and subcortical regions. [Julius, D. MacDermott, A. B., Axel, R. Jessell, T. M. *Science* 241:558-564 (1988).] Studies in several animal species and in humans have shown that the non-selective $5HT_{2C}$ receptor agonist, *meta*-chlorophenylpiperazine (MCPP) decreases food intake. [Cowen, P.J., Clifford, E. M., Williams, C., Walsh, A. E. S., Fairburn, C. G. *Nature* 376: 557 (1995).] Tecott, *et al* have demonstrated that transgenic mice lacking the $5HT_{2C}$ receptor eat more and are heavier than Wild Type mice. [Tecott, L. H., Sun, L. M., Akana, S. F., Strack, A. M., Lowenstein, D. H., Dallman, M. F., Jullus, D. *Nature*

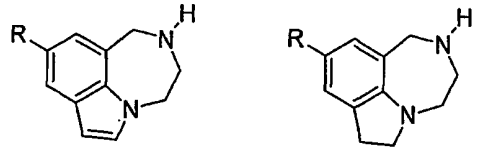
374: 542-546 (1995).] Compounds of this invention are $5HT_{2C}$ receptor subtype selective agonists which are selective over other monoamine receptors, causes a reduction in food intake and result in a reduction in weight gain. Other therapeutic indications for $5HT_{2C}$ agonists are obsessive compulsive disorder, depression, panic disorder, schizophrenia, sleep disorders, eating disorders, and epilepsy.

The non-selective 5-HT_{2c} agonist, *meta*-chlorophenylpiperazine (*m*-CPP), has been shown to block conditioned avoidance responding (CAR) in the rat, an activity usually associated with antipsychotic activity in man [Martin, Gregory E.; Elgin, Jr., Robert J.; Mathiasen, Joanne R.; Davis, Coralie B.; Kesslick, James M.; Baldy, William J.; Shank, Richard P.; DiStefano, Deena L.; Fedde, Cynthia L.; Scott, Malcolm K. *J. Med. Chem.* **1989**, *32*, 1052-1056]. More recently, additional data suggests that 5-HT_{2c} agonism may produce an antipsychotic-like effect in the CAR model [Browning, J. L.; Young, K. A.; Hicks, P. B. Presented at the 29th Annual Meeting of the Society for Neuroscience, Miami Beach, Florida, October 1999, Abstract **830.12**].

United States Patent 3,914,250 (October 21, 1975) describes 1,4-diazepino-[6,5,4-jk]carbazoles, having the structures below, as anticonvulsant agents.



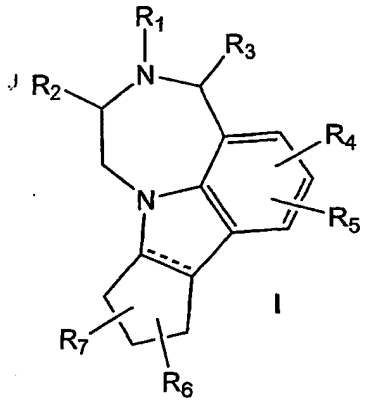
Pyrrolo[3,2,1-*jk*][1,4]benzodiazepines and 4,5-dihydropyrrolo[3,2,1-*jk*][1,4]-benzodiazepines have been described by Hester *et al.* (*J. Med. Chem.* **1970**, *13*, 827-835) to have central nervous system activity.



This invention provides cyclopenta[b][1,4]diazepino[6,7,1-hi]indoles and derivatives which bind to and activate $5HT_{2C}$ receptors in the CNS and are useful for the treatment of CNS disorders which can benefit from modulation of the $5HT_{2C}$ receptor.

DESCRIPTION OF THE INVENTION

This invention provides compounds of formula **I** having the structure:



I

wherein:

R_1 is hydrogen, alkyl of 1-6 carbon atoms, aryl, acyl of 2-7 carbon atoms, or -C(O)R' wherein R' is alkyl of from 1 to 6 carbon atoms or aryl, preferably phenyl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, alkoxy of 1-6 carbon atoms, $-CH_2OH$, fluorinated alkyl of 1-6 carbon atoms, $-NH-SO_2$-alkyl of 1-6 carbon atoms, $-SO_2-NH$-alkyl of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aryl, arylalkyl, heteroaryl, aroyl, or heteroaroyl;

R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of 1-6 carbon atoms, -CN, $-NH-SO_2$-alkyl of 1-6 carbon atoms, $-SO_2-NH$-alkyl of 1-6 carbon atoms, alkylamide of 1-6 carbon atoms (-CO-NHalkyl), amino, alkylamino of 1-6 carbon atoms, dialkylamino of

1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aroyl or heteroaroyl;

R_6 and R_7 are each independently hydrogen, C_1-C_6 alkyl, cycloalkyl of 3 to 7 carbon atoms or $-CH_2$-(cycloalkyl of 3 to 7 carbon atoms);

the dashed line indicates an optional double bond;

or a pharmaceutically acceptable salt thereof.

As used herein alkyl as a group or part of a group, e.g. arylalkyl, alkylamino or alkoxy, etc., includes straight or branched chain alkyl groups of 1-6 carbon atoms; e.g. methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl. Alkoxy groups are for example methoxy, ethoxy, propoxy, isopropoxy and butoxy. Cycloalkyl groups may be for example cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In the definitions used herein, the fluorinated alkyl and fluorinated alkoxy groups indicate the specified alkyl or alkoxy groups, e.g as defined above, having any amount of fluorine substitution including, but not limited to, groups such as $-CHF_2$, $-CF_3$, $-C_2F_5$, $-OCF_3$, etc.

In the definitions used herein aryl as a group or part of a group e.g., arylalkyl has preferably 6-10 carbon atoms, e.g. phenyl or naphthyl, most preferably phenyl. Heteroaryl as a group or part of a group, e.g. heteroaroyl includes mono- or bi-cyclic rings having 5 -10 ring members and 1-3 heteroatoms, the same or different, selected from O, N and S, for example thienyl, furanyl, pyrrolyl, pyridinyl or pyrimidinyl.. In the definitions used herein such as for each of R_2, $R_{2'}$ and R_3 and R_4 and R_5, the aroyl group is preferably benzoyl. The heteroaroyl group is preferably thienoyl. The arylalkyl group is preferably benzyl.

Examples of acyl are alkanoyl groups of 2-7 carbon atoms wherein the alkyl portion is as exemplified above; e.g. acetyl, propionoyl.

In the compounds disclosed herein, including intermediates, the variables when present may have one the following values, or any combination thereof:

R_1 may be for example hydrogen, C_1-C_6 alkyl, benzoyl and alkanoyl of 2-7 carbon atoms.

R_2 may be hydrogen, alkyl or fluorinated alkyl of 1-6 carbon atoms, $-CH_2OH$ or cycloalkyl eg of 5-7 carbon atoms.

R_3 may be hydrogen, alkyl or fluorinated alkyl of 1-6 carbon atoms, $-CH_2OH$ or cycloalkyl eg of 5-7 carbon atoms.

R_4 may be hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, -CN, amino or fluorinated alkyl of 1 to 6 carbon atoms, such as trifluoromethyl; especially hydrogen or alkyl of 1-6 carbon atoms.

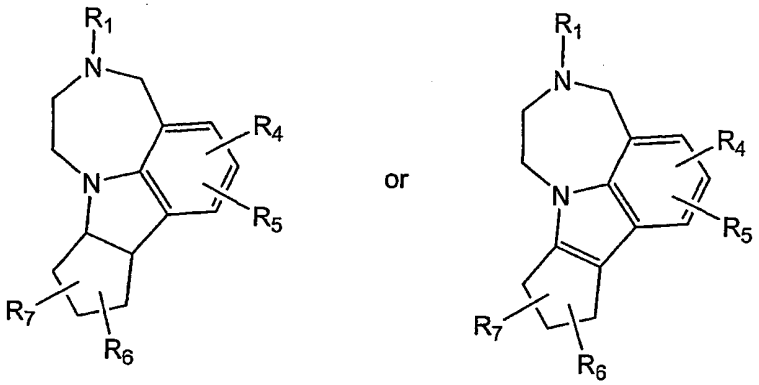
R_5 may be hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, -CN, amino or fluorinated alkyl of 1 to 6 carbon atoms, such as trifluoromethyl; especially hydrogen or alkyl of 1-6 carbon atoms.

R_6 may be hydrogen or alkyl of 1-6 carbon atoms.

R_7 may be hydrogen or alkyl of 1-6 carbon atoms.

The dotted line may be present or absent.

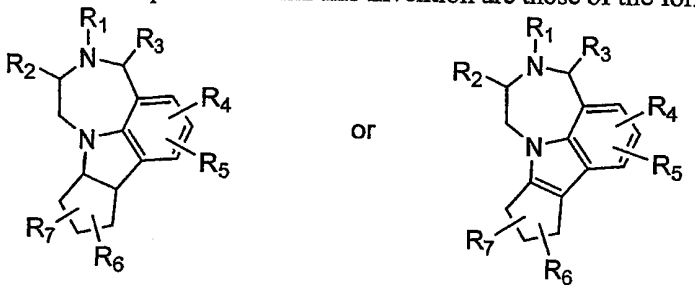
Two groups of compounds within this invention comprise compounds of the formulae:



wherein R_1, R_4, R_5, R_6 and R_7 are as defined hereinabove, or a pharmaceutically acceptable salt thereof. A subset of this group of compounds comprise those in which R_1 is H or alkyl of from 1 to 6 carbon atoms, preferably H or $-CH_3$.

Another preferred group of the compounds are those of the formulae above wherein R_1 and R_7 are hydrogen and R_4, R_5, and R_6 are as defined above, or a pharmaceutically acceptable salt thereof. In a subset of these compounds, R_1, R_4, and R_5 are each hydrogen and R_6 and R_7 are as defined above, or a pharmaceutically acceptable salt thereof. In a further preferred subset R_1, R_4, R_5, and R_6 are hydrogen and R_7 is as defined above.

Another set of compounds within this invention are those of the formulae:



wherein:

R_1 is hydrogen, or alkyl of 1-6 carbon atoms;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl, alkoxy of 1-6 carbon atoms, $-CH_2OH$, or fluorinated alkyl of 1 to 6 carbon atoms, such as trifluoromethyl;

R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, -CN, amino or fluorinated alkyl of 1 to 6 carbon atoms, such as trifluoromethyl;

R_6 and R_7 are each independently hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

The $5HT_{2C}$ receptor agonists of this invention are useful for the treatment or prevention in mammals, preferably in humans, of disorders involving the central nervous system such as obsessive-compulsive disorder, depression, atypical depression, bipolar disorders, anxiety, generalized anxiety disorder, schizophrenia, psychoses, personality disorders, organic mental disorders, behavioral disorders associated with dementia or age-related conditions, aggressivity, drug and alcohol addiction, social phobias, sexual dysfunction, panic disorder, migraine, sleep disorders, such as sleep apnea, eating disorders, such as hyperphagia, bulimia or anorexia nervosa, obesity, epilepsy, and premenstrual tension..

This invention also includes methods of utilizing the compounds herein in treatments or preventative regimens for treatment of central nervous system deficiencies associated with trauma, stroke, neurodegenerative diseases or toxic or infective CNS disorders including, but not limited to, encephalitis or menengitis; or cardiovascular disorders, including thrombosis; gastrointestinal disorders such as malfunction of gastrointestinal motility; and diabetes insipidus. These methods include the improvement or inhibition of further degradation of central nervous system activity during or following the malady or trauma in question. Included in these improvements are maintenance or improvement in motor and motility skills, control, coordination and strength.

This invention includes methods for treating each of these conditions, the methods comprising administering to a mammal in need thereof a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof.

The compounds of this invention contain asymmetric carbon atoms and thus give rise to optical isomers and diastereoisomers. While shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereoisomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

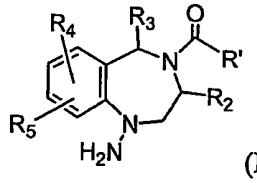
The term "alkyl" includes both straight- and branched-chain saturated aliphatic hydrocarbon groups and cycloalkyl groups. Halogen is defined as Cl, Br, F, and I.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids.

Preferred compounds of this invention are those in which R_1 is hydrogen. Especially preferred are compounds which are enantiomerically pure stereoisomers of compounds where R_1 is hydrogen and the pyrrole ring is reduced.

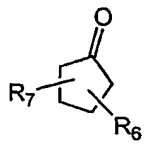
This invention also provides processes for preparing the compounds of formula (I), which processes comprise one of the following:

a) reacting a compound of formula



(II)

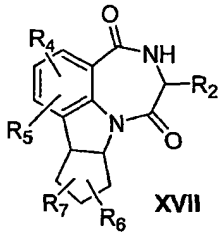
wherein R', R_2, R_3, R_4 and R_5 are as defined above,
with a compound of formula:



wherein R_6 and R_7 are as defined above, and cyclising the resultant hydrazone, to give a corresponding compound of formula (I) wherein R_1 is -C(O)R' and the optional bond is

or

b) reducing a compound of formula



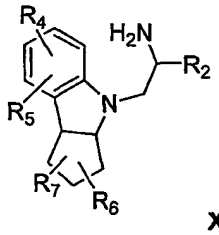
XVII

wherein R_2, R_4, R_5, R_6 and R_7 are as defined above,

with a reducing agent to give a corresponding compound of formula (I) wherein R_3 is hydrogen and the optional bond is absent;

or

c) reacting a compound of formula (XXIV):



XXIV

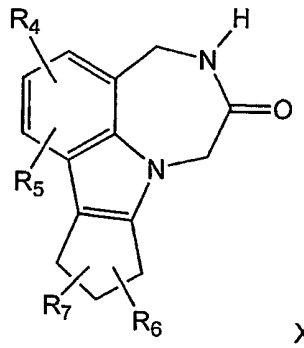
wherein R_2, R_4, R_5,R_6 and R_7 are as defined above, with a compound of formula

R_3CHO

wherein R_3 is as defined above, to give a corresponding compound of formula (I) wherein the optional bond is absent;

or

d) reducing a diazabenzo[*cd*]cyclopenta[*a*]azulen-6-one compound of formula XXXV:



XXXV

wherein R_4, R_5,R_6 and R_7 are as defined above, with a reducing agent to a corresponding compound of formula (I) wherein R_2 is hydrogen;

or

e) reducing a compound of formula (I) wherein the optional bond is present to provide a compound of formula (I) wherein the optional bond is absent;

f) hydrolysing a compound of formula (I) wherein R_1 is acyl or -C(O)R' to give a compound of formula (I) wherein R_1 is hydrogen;

or

g) acylating a compound of formula (I) wherein R_1 is hydrogen with an acylating agent containing the group -C(O)R' to give a compound of formula (I) wherein R_1 is acyl or -C(O)R';

or

h) alkylating a compound of formula (I) wherein R_1 is hydrogen with an alkylating agent containing the group $-R_1$ wherein R_1 is alkyl or aryl to give a compound of formula (I) wherein R_1 is alkyl or aryl;

or

i) removing a protecting group from a compound of formula (I) in which at least one substituent carries a protecting group to give a compound of formula (I);

or

j) converting a basic compound of formula (I) to a salt thereof by reaction with a pharmaceutically acceptable acid or vice versa;

or

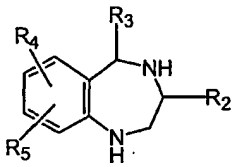
k) converting a compound of formula (I) having one or more reactive substituent groups to a different compound of formula (I);

or

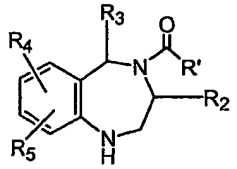
l) isolating an isomer of a compound of formula (I) from a mixture thereof.

With regard to step a) the compound of formula (I) may be prepared by the following reaction sequence comprising the steps a1-a5:

a1) treating a benzodiazepine compound of the formula:

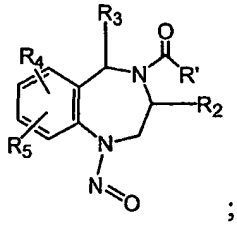


wherein $R_{2'}$, R_2, R_3, R_4 and R_5 are as defined herein; with an acylating agent containing COR' and a base in the presence of a polar solvent, to give an acylated benzodiazepine of the formula:



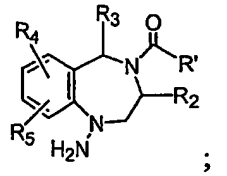
wherein R' represents alkyl of from 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, or a benzyl or naphthyl group;

a2) reacting the acylated benzodiazepine of step a1) with a nitrosating agent to provide an acylated nitroso benzodiazepine compound of the formula:



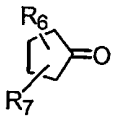
;

a3) reducing the acylated nitroso benzodiazepine compound of step a2) to yield an acylated 1-aminobenzodiazepine compound of the formula

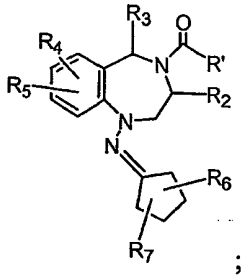


;

a4) reacting the acylated 1-aminobenzodiazepine compound of step 3) to react with a cyclopentanone compound of the formula:

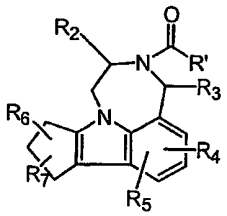


wherein R_6 and R_7 are as defined herein; to provide a cyclopentylideneamino benzodiazepine compound of the formula:



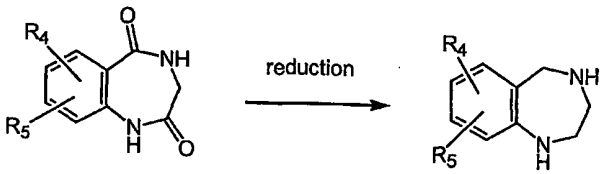
;

a5) cyclising the cyclopentylideneamino benzodiazepine compound of step 4) to provide an acylated compound of the formula:



where in $R_{2'}$, R_2, R_3, R_4, R_5, R_6 and R_7 are as defined herein.

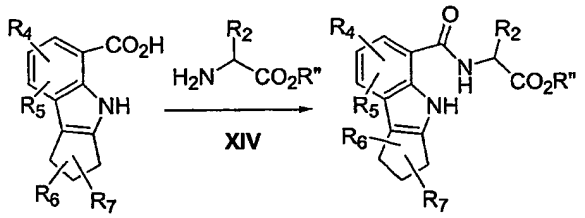
This invention also provides processes for preparing the compounds of the invention wherein the benzodiazepine compound of step a1, above, is initially prepared by reduction of a corresponding substituted or unsubstituted benzodiazepinedione, as shown below.



wherein R_4 and R_5 are as defined herein.

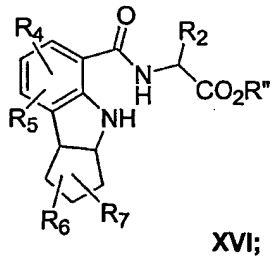
With regard to step b) the compound of formula (I) may be prepared by the following reaction sequence comprising the steps 1-5:

b1) reacting an optionally substituted cyclopentaindole-5-carboxylic acid of the formula **XIII** with an amino acid ester of formula **XIV**, wherein R' represents an alkyl group of from 1 to 10 carbon atoms, to produce an optionally substituted cyclopentaindole-5-carbonyl-amino acetic acid alkyl ester of formula **XV**;



wherein R_2, R_4, R_5, R_6 and R_7 are as defined above and COOR" is an ester group ,

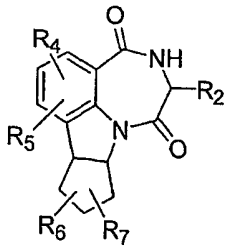
b2) treating the optionally substituted cyclopentaindole-5-carbonyl-amino acetic acid alkyl ester of formula **XV** from step b1) with a reducing agent to provide an optionally substituted cyclopenta[b]indole-5-carbonyl-amino-acetic acid alkyl ester of the formula **XVI**:



XVI;

wherein R_2, R_4, R_5,R_6 and R_7 are as defined above and COOR" is an ester group ,

b3) hydrolysing the reduced ester compound of formula **XVI** in the presence of a base, followed by treatment with an acid, to form an optionally substituted diaza-benzo[*cd*]cyclopenta[a]azulene-4,7-dione compound of formula **XVII**:

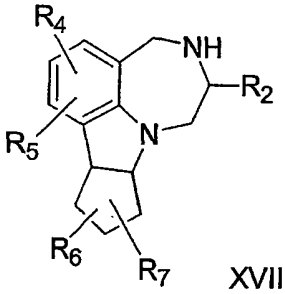


XVII

wherein R_2, R_4, R_5, R_6 and R_7 are as defined above,

and

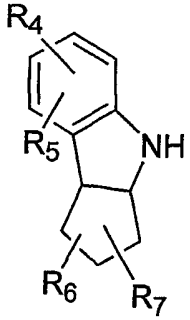
b4) treating the optionally substituted diaza-benzo[*cd*]cyclopenta[a]-azulene-4,7-dione compound of formula **XVII** with a reducing agent to provide a compound of the formula **XVIII**:



XVIII

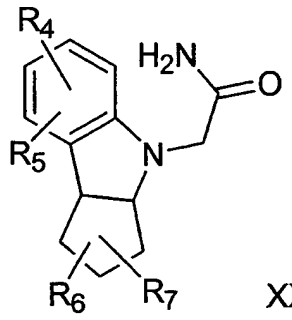
With regard to step c) compounds of formula (I) may be prepared by the following reaction sequence comprising the steps c1)-c5):

c1) converting a cyclopenta[b]indole compound of the formula:



XXII

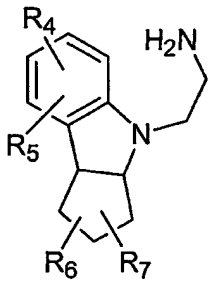
wherein R_4, R_5, R_6 and R_7 are as defined herein; to an optionally substituted cyclopenta[b]indol-4-ylacetamide compound of the formula:



XXIII

wherein R_4, R_5, R_6 and R_7 are as defined herein;

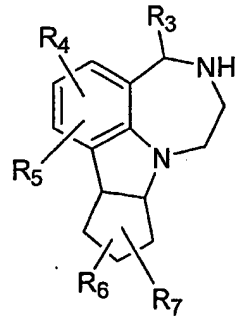
c2) reducing the optionally substituted cyclopenta[b]indol-4-ylacetamide of step c1) to the corresponding optionally substituted cyclopenta[b]indol-4-yl-amine of the formula:



XXIV

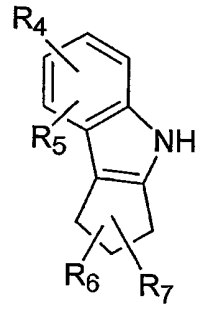
and

c3) cyclizing the cyclopenta[b]indol-4-yl-amine of step c2) to an optionally substituted diaza-benzo[cd]cyclopenta[a]azulene compound of the formula:



XXV

The process above further optionally comprises an initial step wherein the cyclopenta[b]indole compound of step c1) is formed from the reduction of a cyclopenta[b]indole compound of the formula:

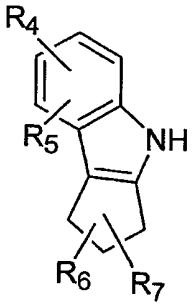


XXI

wherein R_4, R_5, R_6 and R_7 are as defined herein.

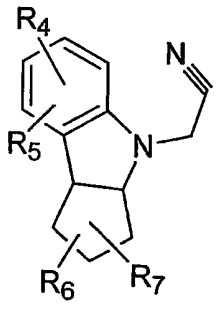
An alternate synthesis of this invention comprises the steps of:

cc1) converting an optionally substituted cyclopenta[b]indole compound of the formula:



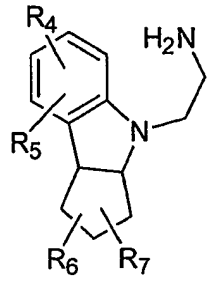
XXII

to produce an optionally substituted nitrile compound of the formula:



XXIIIa

cc2) reducing the optionally substituted nitrile compound of step aa1) to provide an optionally substituted amine compound of the formula:



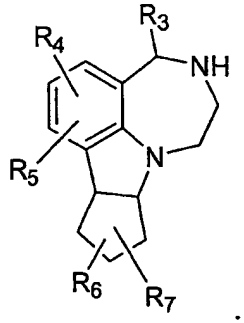
;

and

cc3) cyclizing the amine compound of step cc2) using an aldehyde of formula:

R_3CHO

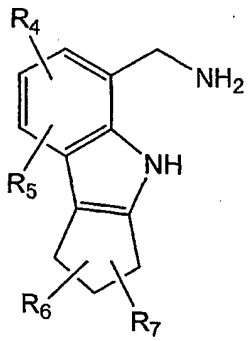
to give an optionally substituted diaza-benzo[cd]cyclopenta[a]azulene compound of the formula:



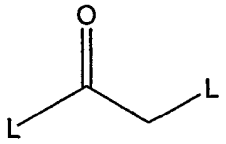
wherein R_3, R_4, R_5, R_6 and R_7 are as defined herein.

With regard to step d) compounds of formula **XXXV** may be prepared by a process comprising the steps of:

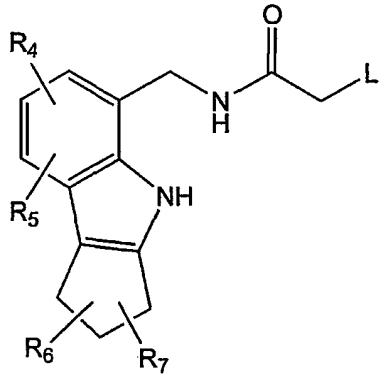
d1) acylating a cyclopentaindole methylamine of the formula:



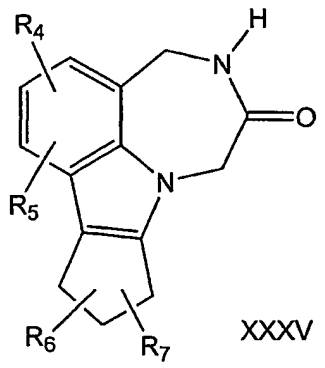
wherein R_4, R_5, R_6 and R_7 are as defined above, with an acylating agent of the formula:



wherein L represents a leaving group as known in the art, such as a halogen, preferably Br, Cl or I, to produce an acylated compound of the formula:



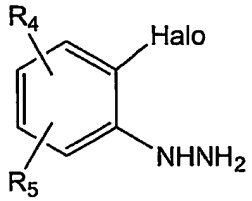
d2) cyclizing the acylated compound of step d1), e.g., by treating with a suitable base in the presence of a polar solvent, to produce an optionally substituted diazabenzo[*cd*]cyclopenta[*a*]azulen-6-one compound of the formula:



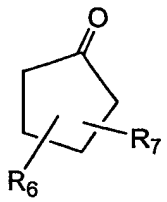
XXXV

It will be understood that the beginning optionally substituted cyclopenta-indolemethylamine compounds of step d1), above, may be prepared by a number of synthetic methods known in the art. Additional steps within the scope of this invention for the preparation of this compound include:

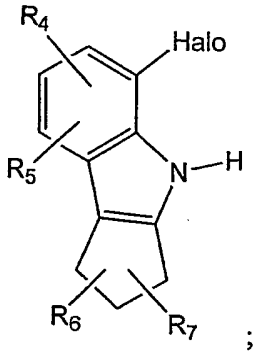
dd1) allowing an optionally substituted 2-halophenylhydrazine compound of the formula:



wherein Halo represents a halogen, preferably Br or I, and R_4 and R_5 are as defined above, to react with an optionally substituted cyclopentanone compound of the formula:

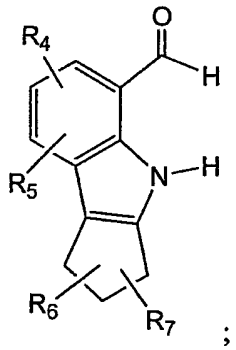


wherein R_6 and R_7 are as defined above, to produce a 5-halo-cyclopenta[*b*]indole compound of the formula:



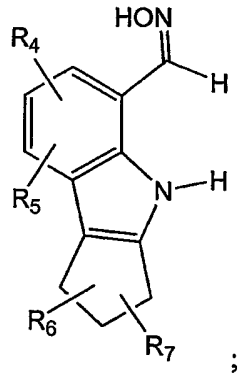
;

dd2) converting the 5-halo-cyclopenta[*b*]indole compound of step dd1) to an optionally substituted cyclopenta[b]indole aldehyde of the formula:



;

dd3) converting the optionally substituted cyclopenta[*b*]indole aldehyde of step dd2) to a corresponding optionally substituted cyclopenta[*b*]indole-5-carbaldehyde oxime of the formula:

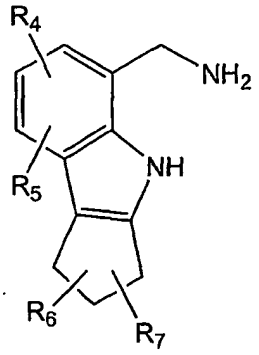


;

and

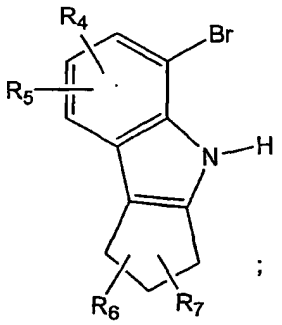
dd4) treating the optionally substituted cyclopenta[*b*]indole-5-carbaldehyde oxime of step dd3) with a reducing agent to provide a cyclopentaindole methylamine of

the formula:



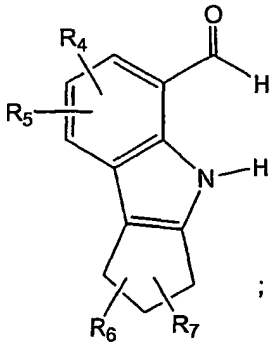
wherein R_4, R_5, R_6 and R_7 are as described above.

This invention also provides novel compounds which may be used as intermediates in the production of the pharmaceutically useful compounds described herein. These compounds include those of the formulae:



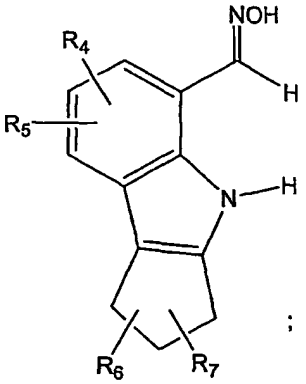
;

IV



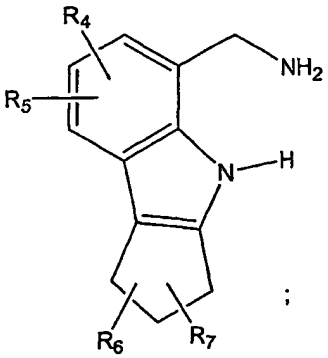
;

V



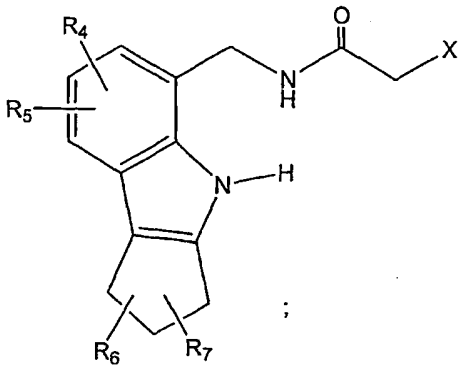
;

VI

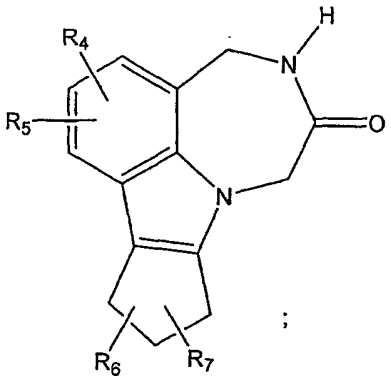


;

VII



IX



X

wherein in each formula R_4, R_5, R_6 and R_7 are as defined above and in Formula **IX**, the moiety X is Cl, Br or I. Subsets of the intermediate compounds of Formulas **IV**, **V**, **VI**, **VII**, **IX** and **X** which may be prepared by the processes described herein include those in which each of R_4, R_3, R_6 and R_7 are hydrogen. Another group of compounds of this invention include those in which R_4 is hydrogen and R_5, R_6 and R_7 are as defined above. In another group, R_4 and R_6 are hydrogen and R_5 and R_7 are as defined above. A further group of this invention comprises those compounds in which R_4, R_5, and R_6 are hydrogen and R_7 is as defined above.

Among the more preferred compounds of these groups are:

5-Bromo-1,2,3,4-tetrahydro-cyclopenta[*b*]indole;

5-Bromo-3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole;

5-Bromo-2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole;

5-Bromo-1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole;

1,2,3,4-Tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde;

3-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde;

2-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde;

1-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde;

1,2,3,4-Tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime;

3-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime;

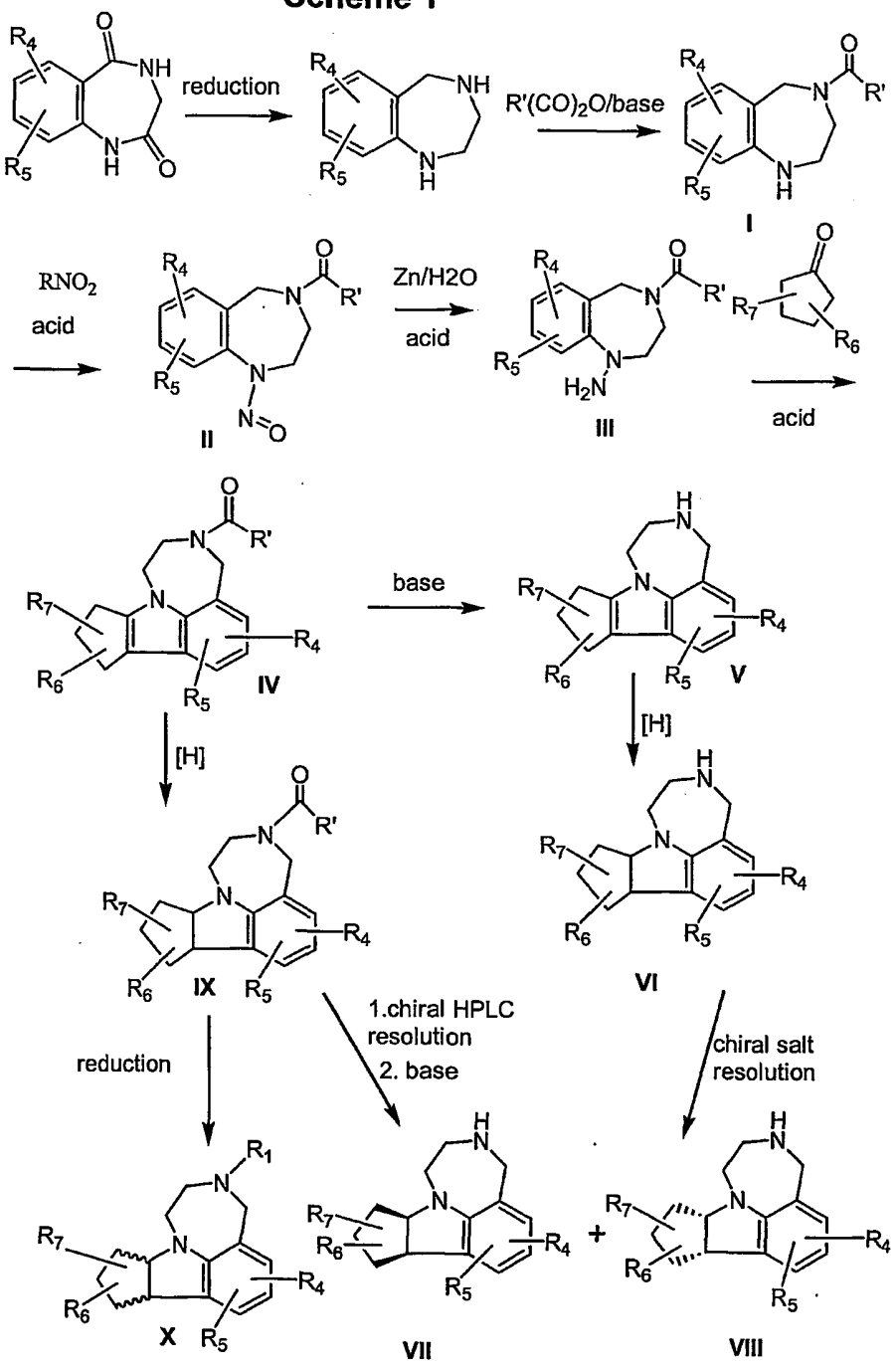
2-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime;

1-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime;
C-(1,2,3,4-Tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine;
C-(3-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine;
C-(2-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine;
C-(1-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine;
2-Chloro-*N*-(1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Chloro-*N*-(3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Chloro-*N*-(2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Chloro-*N*-(1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Iodo-*N*-(1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Iodo-*N*-(3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Iodo-*N*-(2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Iodo-*N*-(1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
4,5,9,10-Tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one;
8-Methyl-4,5,9,10-tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one;
9-Methyl-4,5,9,10-tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one; and
10-Methyl-4,5,9,10-tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one.

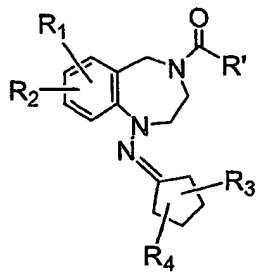
More specifically, the compounds of this invention can be prepared according to the following scheme from commercially available starting materials or starting materials which can be prepared using literature procedures.

Scheme 1 shows the preparation of representative compounds of this invention.

Scheme 1


reduction
R'(CO)2O/base
RNO2
acid
Zn/H2O
acid
acid
base
[H]
[H]
1.chiral HPLC
resolution
2. base
chiral salt
resolution
reduction
I
II
III
IV
V
VI
VII
VIII
IX
X

In Scheme 1, a substituted or unsubstituted benzodiazepinedione is reduced with a reducing agent, such as lithium aluminum hydride or a borane-tetrahydrofuran complex, to give a substituted or unsubstituted benzodiazepine. The basic nitrogen of the benzodiazepine is acylated with an acylating reagent , such as an acid anhydride, in the presence of a base, such as triethylamine, in an organic solvent, such as ether, to give intermediate I. Intermediate I is allowed to react with an organic or inorganic nitrosating agent, such as t-butyl nitrite or sodium nitrite, in the presence of an acid, such as acetic acid or hydrochloric acid, to give nitroso compounds II. The nitroso compounds are reduced to hydrazines III using a reducing agent, such as zinc powder in acetic acid and water. The hydrazines III are allowed to react with substituted or unsubstituted cyclopentanones in acid, such as acetic acid at 25-110 °C, to give substituted or unsubstituted hydrazones of formula

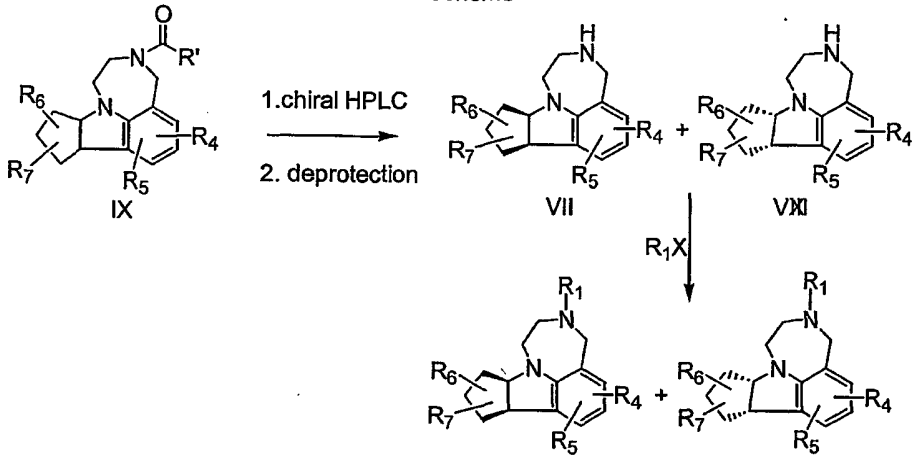


IV

The hydrazones are treated with an acid, such as sulfuric acid or p-toluenesulfonic acid, in the presence of water or an alcohol, such as 1-propanol, at elevated temperatures such as 50-110 °C to give protected fused. indoles IV. The fused indoles IV can be treated with a base, such as NaOH, in a polar solvent, such as water or an alcohol, to give the fused indoles V, which are products of this invention. In addition, fused indoles V can be reduced, such as by catalytic hydrogenation over a catalyst, such as palladium on charcoal, in an organic solvent, such as ethanol, in the presence of a trace of acid, such as trifluoroacetic acid, to give fused indolines VI which are products of this invention. Alternatively, fused indoles IV can be reduced, such as by catalytic hydrogenation over a catalyst, such as palladium on charcoal, in an

organic solvent, such as ethanol, in the presence of a trace of an acid, such as trifluoroacetic acid, to give fused indolines **IX**. Fused indolines **IX** are racemic mixtures which can be resolved using chiral HPLC to give separated enantiomers which can then be treated with an inorganic base, such as NaOH in a polar solvent, such as water or methanol at elevated temperatures, such as 50-100 °C, to remove the acyl group giving enantiomers **VII** and **VIII** which are products of this invention. Finally, fused indolines **IX** can be reduced with a reducing agent, such as a borane tetrahydrofuran complex, to give fused indolines **X**, which are compounds of this invention. Enantiomers **VII** and **VIII** can also be obtained by chiral salt resolution of racemic fused indolines **VI** using a resolving agent, such as benzoyltartaric acid, in an organic solvent, such as an alcohol. As shown in the Scheme below treatment of the secondary amine of **VII** and **VIII** with an alkylating agent R_1X, such as an alkyl halide, gives the corresponding alkyl derivatives which are compounds of this invention.

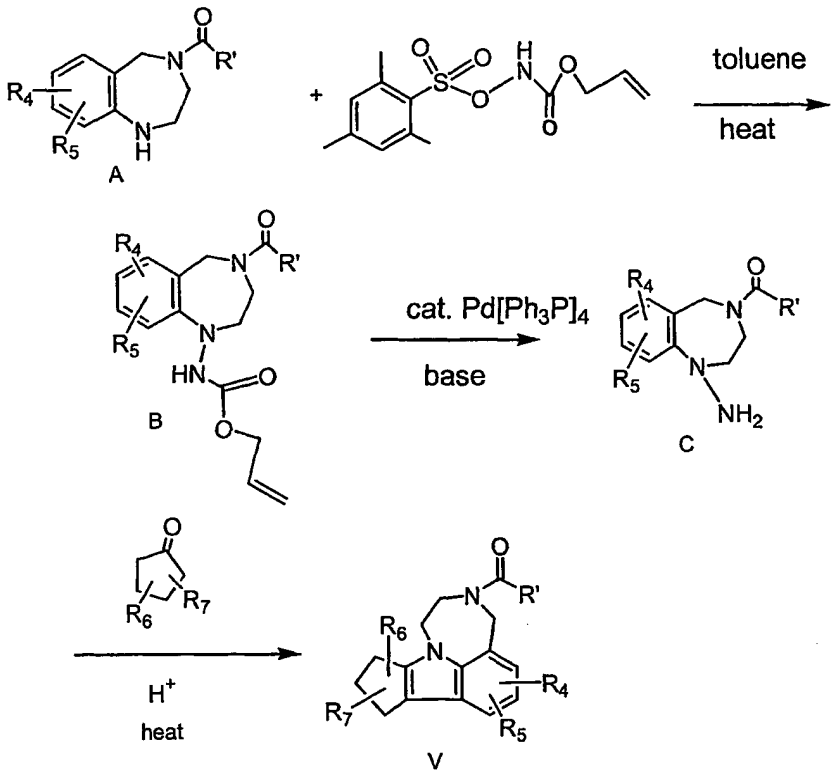
Scheme



An alternate syntheic route to hydrazines **III** is described in Scheme **1A**. Substituted or unsubstituted benzodiazepines **I** are allowed to react with allyl N-[(mesitylsulfonyl)oxy]carbamate in toluene under reflux to give compounds **XII**. Compounds **XII** are allowed to react with a catalytic amount of tetrakis triphenylphosphinepalladium and a base, such as diethylamine, in an organic solvent,

such as methylene chloride, to give hydrazines **III**. Hydrazines **III** are converted to fused indoles **V** as described in Scheme **1A**:

Scheme 1A

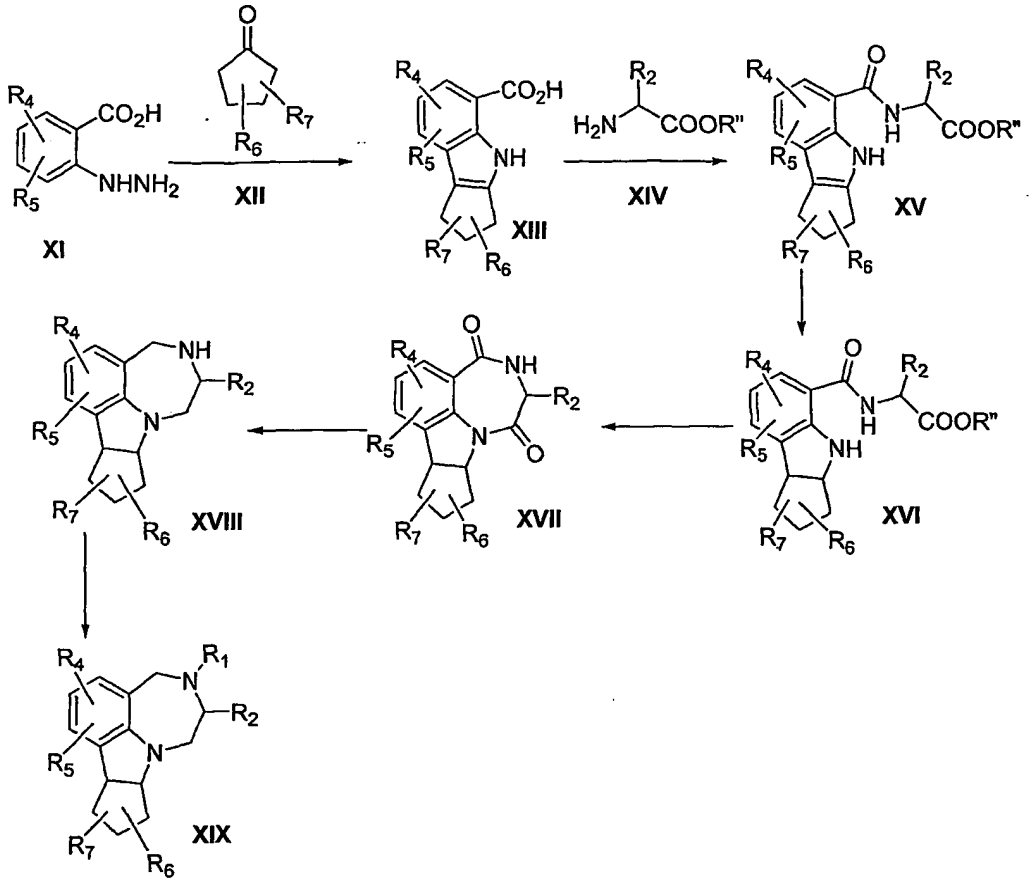


An alternate route to hydrazones **IV** is where substituted or unsubstituted benzodiazepines **I** are allowed to react with an inorganic cyanate, such as sodium cyanate, in an organic solvent, such as acetonitrile, in the presence of an acid, such as trifluoroacetic acid, at elevated temperatures, such as 35-75 °C to give a urea. Thue urea is treated with an inorganic hypochlorite, such as sodium hypochlorite, in an alcohol-water solution at 0-25 °C to give hydrazines **III**. Hydrazines **III** in solution are cooled to <25°C and treated with acetic acid and substituted or unsubstituted cyclopentanones and warmed to room temperature to give hydrazones **IV**. Hydrazones **IV** are converted to fused indoles **V** as described in Scheme 1.

It will be understood that the processes of this invention can further include analogous steps wherein the protecting group applied to the optionally substituted benzodiazepines of Formula I in Scheme 1 are other than the acetyl group used above. Other conventional protecting groups known in the art may also be used including, but not limited to alkyl and acyl chlorides, alkyl or aryl chloroformates, such as ethylchloroformate and benzyl chloroformate and dialkylcarbonates, and para-nitro benzene sulfonyl chloride.

Compounds of this invention were also prepared according to the following Scheme 2 from commercially available starting materials or starting materials which can be prepared using literature procedures.

Scheme 2



In **Scheme 2**, a 2-hydrazinobenzoic acid **XI** is allowed to react with a ketone **XII** under standard Fischer-indole conditions. The reaction is carried out in the presence of an acid, such as sulfuric acid or acetic acid, with or without a solvent, such as water or ethanol, at a temperature above ambient temperature, such as 30-150°C.

The resulting indole-carboxylic acid **XIII** is coupled with an amino acid ester **XIV**, such as L-alanine methyl ester, in the presence of peptide coupling reagents, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole hydrate (HOBt), and a base, such as diisopropylethylamine, in an inert organic solvent, such as dichloromethane.

. It will be understood that the amino acid ester **XIV** may comprise any known in the art to be used in cyclization procedure as disclosed in Scheme 2. Among the

most preferred are those wherein R" in formula **XIV** are represent alkyl groups of from 1 to 10 carbon atoms, either straight, branched or cyclic. Among the most preferred are the shorter chain esters, such as the methyl, ethyl, isopropyl, n-propyl, n-butyl, and t-butyl esters.

The resulting indole-amide **XV** can be reduced to indoline-amide **XVI** by catalytic hydrogenation in the presence of a metal catalyst, such as 5% Pd/C or by a hydride source, such as triethylsilane or borane, in the presence of an acid, such as trifluoroacetic acid.

The indoline-amide **XVI** can be cyclized to the bislactam **XVII** by hydrolysis of the ester with a base, such as lithium hydroxide, and subsequent treatment with an acid, such as acetic acid.

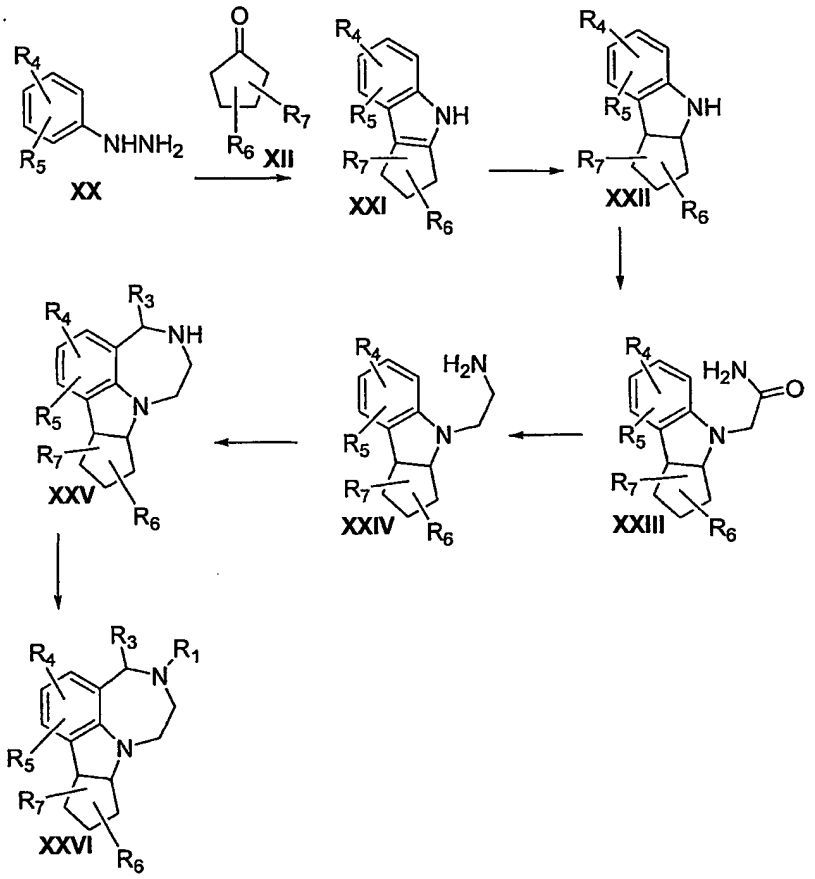
The bislactam **XVII** can be reduced to the benzodiazepine **XVIII**, which are compounds of this invention, with a reducing agent, such as borane or lithium aluminum hydride, in the presence of an inert organic solvent, such as tetrahydrofuran.

When $R_1 \neq H$, reaction of benzodiazepine **XVIII** with an alkyl halide, such as methyl iodide, or an acyl halide, such as acetyl chloride, or an aroyl chloride, such as benzoyl chloride, gives **XIX** which are also compounds of this invention.

An alternative synthetic route to compounds of this class is depicted in **Scheme 3**. An arylhydrazine **XX** is allowed to react with a ketone **XII** under standard Fischer-indole conditions. The reaction is carried out in the presence of an acid, such as sulfuric acid or acetic acid, with or without a solvent, such as water or ethanol, at a temperature above ambient temperature, such as 30-150 °C.

The resulting indole **XXI** can be reduced to indoline **XXII** by catalytic hydrogenation in the presence of a metal catalyst, such as 5% Pd/C or by a hydride source, such as triethylsilane or borane, in the presence of an acid, such as trifluoroacetic acid.

Scheme 3



The indoline **XXII** can be coupled with an appropriate electrophile, such as chloroacetamide (depicted), or a corresponding synthetic equivalent such as chloroacetonitrile, etc. in the presence of a base, such as diisopropylethylamine or potassium hydroxide, in a suitable solvent, such as DMF or DMSO to give the amide **XXIII**.

The amide **XXIII** can be reduced to the amine **XXIV** with a reducing agent, such as borane or lithium aluminum hydride, in the presence of an inert organic solvent, such as tetrahydrofuran.

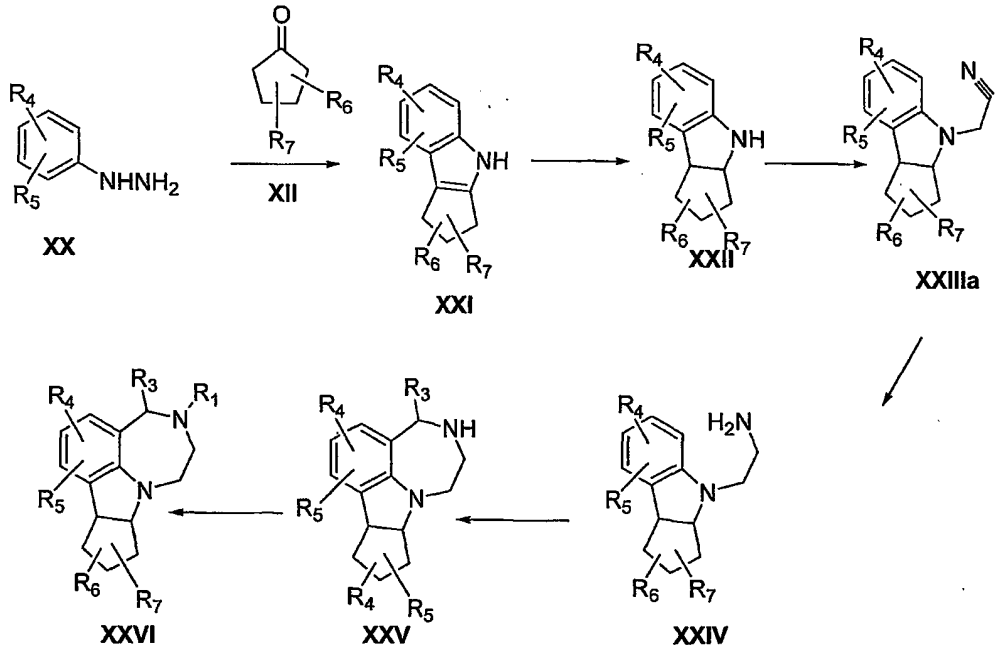
The amine **XXIV** can be cyclized to the benzodiazepine **XXV**, which are compounds of this invention, by treatment with an aldehyde, such as formaldehyde or

acetaldehyde, in the presence of an acid, such as trifluoroacetic acid, in a suitable solvent, such as ethanol, at room temperature or elevated temperatures.

When $R_1 \neq H$, reaction of benzodiazepine **XXV** with an alkyl halide, such as methyl iodide, or an acyl halide, such as acetyl chloride, or an aroyl chloride, such as benzoyl chloride, gives **XXVI** which are also compounds of this invention.

A process of this invention is illustrated in **Scheme 3A** below:

Scheme 3A

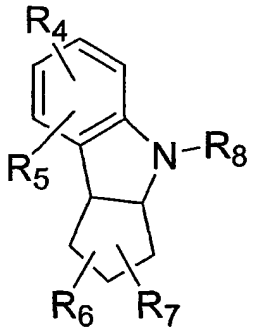


In this alternative route, indoline **XXII** can be coupled with an appropriate electrophile, such as chloroacetonitrile, or a corresponding synthetic equivalent, in the presence of a base, such as diisopropylethylamine or sodium hydride, in a suitable solvent, such as DMF or DMSO to give the nitrile **XXIIIa**.

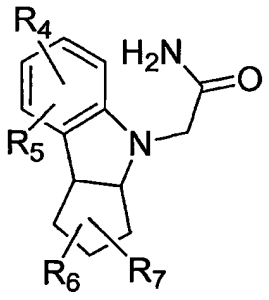
The nitrile **XXIIIa** can be reduced to the amine **XXIV** with a reducing agent, such as borane or lithium aluminum hydride, in the presence of an inert organic

solvent, such as tetrahydrofuran. The nitrile **XXIIIa** can also be reduced to the amine **XXIV** by hydrogenation in the presence of a catalyst, such as palladium, in a suitable solvent, such as ethanol or ethyl acetate.

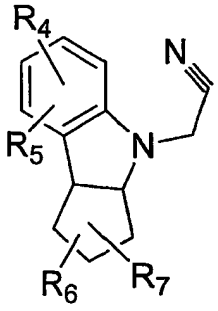
This invention also provides novel groups of compounds useful in the synthesis of the pharmaceutically useful compounds of Formula I described above. These compounds are of the general formula **XXIIa,** including **XXIII, XXIIIa** and **XXIV**:



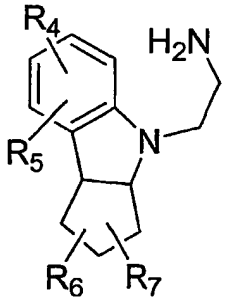
XXIIa



XXIII



XXIIIa



XXIV

in which formulae R_8 is $-CH_2-C(O)-NH_2$, $-CH_2-CN$ or $-CH_2-CH_2-NH_2$; and R_4, R_5, R_6 and R_7 are as defined herein.

For example wherein R_4, R_5, R_6 and R_7 are each, independently, hydrogen, hydroxy, alkyl of 1-6 carbon atoms, cycloalkyl, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of from 1 to 6 carbon atoms, -CN, $-NH-SO_2$-alkyl of 1-6 carbon atoms, $-SO_2-NH-$ alkyl of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6

carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aryl or aroyl. A subset of these compounds includes those in which R_4 and R_5 are hydrogen, and R_6 and R_7 are as defined above. A further subset of these compounds are those in which R_4, R_5 and R_6 are hydrogen, and R_7 is as defined above. Preferred specific compounds are

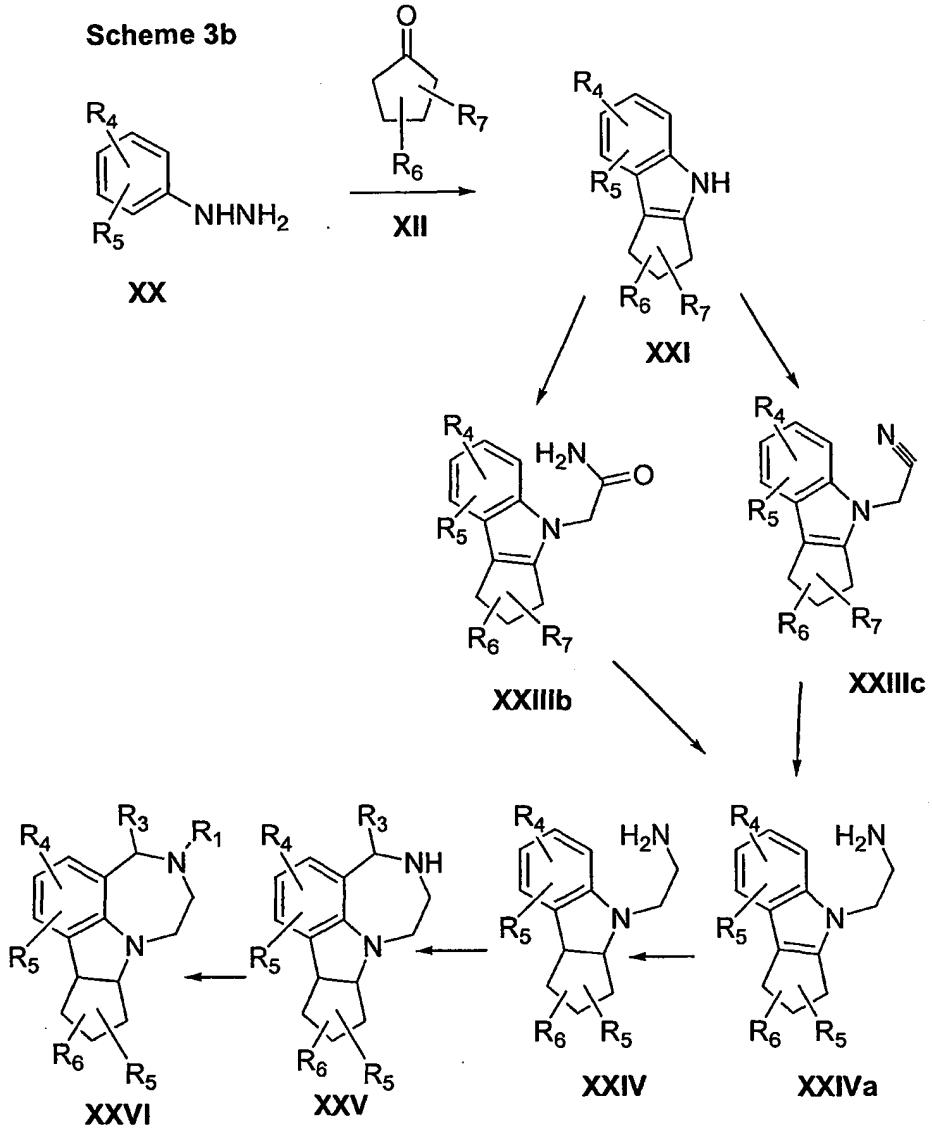
2-(2,3,3a,8b-Tetrahydro-1*H*-cyclopenta[*b*]indol-4-yl)-acetamide,

2-(2,3,3a,8b-Tetrahydro-1*H*-cyclopenta[*b*]indol-4-yl)-acetonitrile,

2-(2,3,3a,8b-Tetrahydro-1*H*-cyclopenta[*b*]indol-4-yl)- ethylamine,

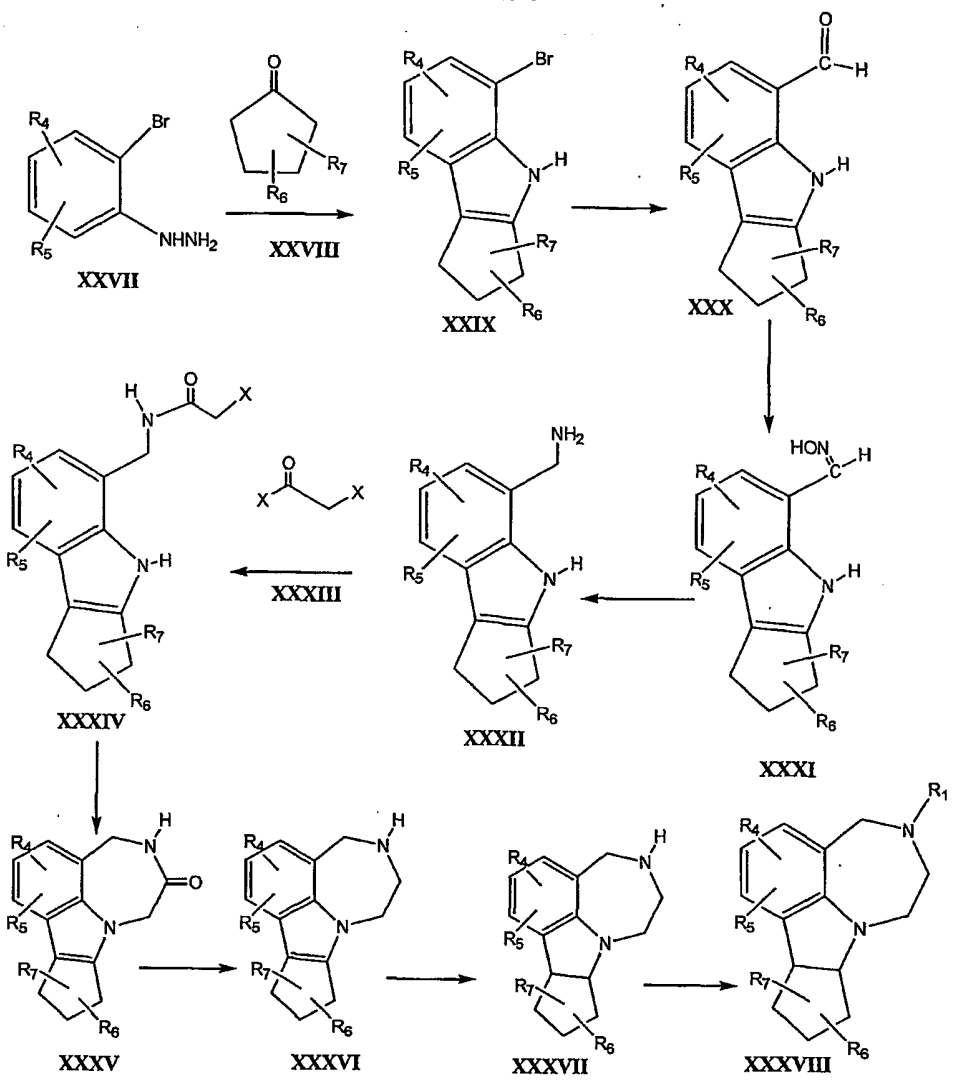
An alternate synthetic route within the scope of this invention is indicated by **Scheme 3b**, which shares the initial and final steps disclosed in **Schemes 3 and 3a**. In this method, rather than reducing the indole **XXI** to indoline **XXII**, as done in **Scheme 3**, the indole **XXI** is directly converted to the corresponding amide **XXIIIb** or nitrile **XXIIIc**, which can then be reduced to the corresponding amines **XXIVa** and **XXIV**.

Scheme 3b



A further process for synthesizing compounds of this invention is presented in **Scheme 4**, wherein R_1, R_4, R_5, R_6 and R_7 are as defined above.

Scheme 4



A 2-bromophenylhydrazine **XXVII** is allowed to react with a ketone **XXVIII** under standard Fisher-indole conditions. The reaction is carried out in the presence of an acid, such as sulfuric acid, acetic acid, or *p*-toluenesulfonic acid with or without a solvent, such as water, alkyl alcohol of 1-6 carbon atoms or dimethylforamide (DMF), at a temperature above ambient temperature, such as 30-150 °C.

The resulting bromoindole **XXIX** may then be lithiated with reagent such as *n*-butyl lithium and formylated with formyl transfer agents such as DMF, N-formyl morpholine or ethyl formate in an acceptable solvent such as diethyl ether (Et_2O) or methyl *t*-butyl ether (MTBE) from -78 °C to ambient temperature.

The resulting indole aldehyde **XXX** is converted to an indole oxime **XXXI** using reagent such as hydroxylamine, N- or O-benzyl protected hydroxylamine in the presence of a suitable base such as pyridine or triethylamine (TEA) in a suitable solvent such as pyridine, water or tetrahydrofuran (THF).

The resulting indole oxime **XXXI** can be reduced to indole amine **XXXII** using a hydride source such as lithium aluminum hydride (LAH) or by catalytic hydrogenation in the presence of a metal catalyst such as palladium on carbon (Pd/C) or Raney nickel.

The resulting indole amine **XXXII** can be acylated with acid halide **XXXIII**, wherein X is an acceptable leaving group, preferably a halogen, such as chloroacetyl chloride in the presence of a base such as pyridine or TEA in a suitable solvent such as methylene chloride.

The resulting acyl indole **XXXIV** can be cyclized to indole amide **XXXV** in the presence of a suitable base such as sodium hydride (NaH), potassium hydride (KH) or lithium hydride (LiH) in the presence of a polar solvent such as THF, dimethylacetamide (DMA) or DMF.

Indole amide **XXXV** can be reduced to benzodiazepine indole **XXXVI** with reagents such as borane, LAH in a suitable solvent such as THF, Et_2O or MTBE. Reduction of benzodiazepine indole **XXXVII**

Reaction of benzodiazepine **XXXVII** with an alkyl halide of 1-6 carbon atoms such as methyl iodide, or an acyl halide, such as acetyl chloride, or an aroyl chloride, such as benzoyl chloride gives benzodiazepine **XXXVIII**.

The acylation steps of this invention are understood to include reactions of the appropriate compound with any acylating agent and reaction conditions known in the art. Useful in these steps are acylating agents include acid halides and esters or anhyrides of the appropriate aliphatic carboxylic acid. Useful acid halides include acetyl chloride, propionyl chloride, isobutyryl chloride, benzoyl chloride, etc. Acid anhydrides include acetic anhydride and benzoic anhydride. Similarly, alkylation steps herein are understood to include any relevant alkylating agents and conditions known in the art. These include, but are not limited to the use of alkyl halides, such as methyl iodide, or alkyl tosylates or aldehyde alkylating agents in the presence of an applicable reducing agent.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, napthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known pharmaceutically acceptable acids. The processes herein will be understood to include an optional additional step of forming a salt form of the products via standard addition reactions with any pharmaceutically acceptable organic or inorganic acid.

This invention also provides a method for resolving the enantiomers of the compounds described herein. A method of resolving the (R,R) enantiomer of these compounds comprises the steps of:

a) dissolving about 1 equivalent of the racemic compound mixture of a product of this invention in a solubilizing amount of an alcohol resolving agent at a temperature of from about 50°C to the reflux temperature for the alcohol, preferably

between about 50°C and 70°C, under an inert atmosphere, to create a resolving solution;

b) treating the resolving solution of step a) with from about 0.1 to about 0.35 equivalents of dibenzoyl-L-tartaric acid, preferably from about 0.15 equivalents to about 0.3 equivalents, more preferably from about 0.23 to about 0.27 equivalents, most preferably about 0.25 equivalents to precipitate the desired (R,R) enantiomer from the resolving solution as the corresponding tartaric acid salt form; and

c) separating the desired enantiomer from the resolving solution through conventional means, such as filtration.

It will be understood that this process may be followed by additional steps of filtration and purification to enhance the purity and yield of the desired enantiomer product in question.

In step b) it is preferred that the temperature of the resolving solution be maintained at a temperature at or above about 50°C, preferably nearer to the reflux temperature of the alcohol in question.

The alcohol component of step a) may be comprise a single alcohol or a combination of two or more alcohols selected from those known in the art into which the compound in question can be dissolved. Among the preferred alcohols are the commercially available and relatively low boiling alcohols comprising 10 carbon atoms or less including methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, *t*-butanol, cyclohexanol, etc.

It will also be understood that the (S,S) enantiomer of the racemic mixture mentioned above could then be purified and collected from the remaining resolving solution described above after collection of the (R,R) tartaric acid salt.

This invention also provides an analogous method for resolving the (S,S) enantiomer from the racemic mixtures of compounds of this invention, the method comprising the steps a) through c) listed above, with dibenzoyl-D-tartaric acid being used in place of dibenzoyl-L-tartaric acid in step b). Comparably, the (R,R) enantiomer

can be collected and purified by conventional means from the remaining solution after the tartaric acid salt form of the (S,S) enantiomer is precipitated and removed in this analogous method.

This invention also comprises pharmaceutical compositions and formulations utilizing the compounds described herein, comprising a pharmaceutically or therapeutically effective amount of one or more compounds of this invention, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

The compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water

(partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

A pharmaceutically or therapeutically effective amount of the compounds herein is understood to comprise an amount of the compound(s) in question which will

obtain at least a minimum of desired effect in preventing, treating, inhibiting or managing the symptoms or causes of the malady in question. More preferably, the amount will be the minimum needed to alleviate or remove the undesirable physiological consequences of the malady in question and inhibit or prevent their re-occurrence.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily dosages of active compound would be 0.02 μg/kg - 750 μg/kg. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packaged powders, vials, ampoules, pre filled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. It will be understood that the dosage administered will be determined by a skilled medical professional taking into account the needs and physical characteristics of the recipient and the nature and extent of the malady to be treated or prevented.

The following provides the preparation of compounds representative of this invention.

Example 1

1,2,3,4,9,10-Hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

A. 3-Acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

4-Acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (8.92 g, 46.9 mmol) was dissolved in water (110 mL) and conc. HCl (6 mL). The solution was cooled in an ice bath and a solution of $NaNO_2$ (3.20 g) in water (10 mL) was added dropwise over 10 min with stirring. After stirring an additional 20 min the solution was extracted with methylene chloride. The organic phase was dried (K_2CO_3), filtered, and the volatiles were removed by evaporation under reduced pressure to give a residue. The residue was dissolved in glacial acetic acid (80 mL), cooled in an ice bath. Powdered zinc (23 g) was added portionwise over 10 min while keeping the reaction temperature below 30°C. Ater stirring for an additional 1.5 h, the reaction mixture was filtered through a pad of Celite. After washing the Celite with glacial acetic acid, cyclopentanone (20 g, 952 mmol, 20 equiv.) was added to the combined filtrates and the reaction mixture was heated (oil bath, 90-105°C) for 2 h with stirring and then allowed to cool to room temperature and stir overnight.

Removal of the acetic acid by evaporation under reduced pressure, gave a residue which was partitioned between 2.5 N NaOH and ethyl acetate. The aqueous phase was extracted with additional ethyl acetate (3X) and the combined extracts were dried and evaporated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel eluting with 1-2% methanol in methylene chloride to give, 2.36 g (9.36 mmol.) of intermediate A, 3-acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole , as a viscous oil.

Intermediate A (2.34g , 9.20 mmol) was dissolved in MeOH . The solution was diluted with 2.5N NaOH and solid NaOH pellets were added. The reaction mixture was placed in an oil bath at 95 °C for 6 h. then cooled to room temperature and stirred

overnight. The volatiles were evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The ethyl acetate was separated and evaporated and the residue was dissolved in methylene chloride and purified by chromatography on silica gel eluting with 2-5% methanol in methylene chloride to give the product of Example 1 as a light gray solid 1.56g (80%) , mp: 66-68 °C.

Anal. Calcd. for $C_{14}H_{16}N_2$

Theory: %C, 79.21; %H, 7.60; %N, 13.20.

Found: %C, 78.81; %H, 7.5 ; %N, 13.10

Example 2

1,2,3,4,8,9,10,10a-Octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

Method A.

The compound of Example 1 (1.56g, 7.35 mmol) was dissolved in trifluoro-acetic acid (53 mL) and cooled in an ice/water bath. 1.5 M BH_3 in THF (34 mL) was added dropwise slowly and stirred for an additional 15min. after the addition was complete. Water was added slowly to quench the reaction followed by 2.5 N NaOH and 50% NaOH until the reaction mixture was basic (yellow color disappeared). After extraction with ethyl acetate (3X), the organic phase were combined and concentrated under reduced pressure to give a residue which was purified by chromatography on silica gel eluting with 3-10% MeOH in methylene chloride to give 600mg (38%) of the product as a yellow solid: mp 64-68 °C.

Anal. Calcd for $C_{14}H_{18}N_2 \cdot 0.2\ H_2O$

Calcd: %C, 77.17; %H, 8.51; %N, 12.86.

Found: %C, 77.13; %H, 8.18; %N, 12.61.

Method B.

3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]-indole

Intermediate A of Example 1 (2.07g, 8.12 mmol) was dissolved in EtOH and hydrogenated over 10% Pd on carbon (0.25g) in a Parr shaker at 55 lbs of hydrogen pressure. After 5 hrs, the reaction mixture was filtered through Celite to remove the catalyst and the filtrate was concentrated under reduced pressure to give a residue which was purified by chromatography on silica gel eluting with 0.3-2% MeOH in methylene chloride to give 1.84g (87%) of 3-acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole as a white solid, mp:111-113 °C.

Anal. Calcd for $C_{16}H_{20}N_2O$ + .20 H_2O

Theory: %C, 73.93; %H, 7.91; %N, 10.78.

Found: %C, 74.05; %H, 7.91; %N, 10.79.

3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole was dissolved in conc. HCl and heated with stirring in an oil bath (110°C) for 12 hr. After cooling, the reaction mixture was made basic with 2.5N NaOH and 50% NaOH, extracted into methylene chloride, dried ($MgSO_4$), filtered and concentrated to give a residue. The residue was purified by chromatography on silica gel eluting with 1-20% MeOH in methylene chloride to give the product as a yellow solid, mp: 76-79°C.

Example 3

The compound of Example 2 was chromatographed on a Chiral column eluting with MeOH containing 0.1% diethylamine.

Peak one was obtained as a yellow solid, mp: 51-54°C and identified (7bS,10aS)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]-indole

Anal. Calcd for $C_{14}H_{18}N_2$ +0.20 H_2O

Theory: %C, 78.46;%H, 8.47;%N, 13.07.

Found: %C, 77.09;%H, 8.50;%N, 12.72.

Peak two was obtained as a yellow solid, mp: 43-46 °C. This peak was identified as a mixture of 92.3% (7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]indole and 7.7% of identified (7bS,10aS)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole.

Example 4

3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole was chromatographed on a Chiralcel AD chiral column (20 x 250 mm) eluting with 100% MeOH at room temperature, detection method: UV/VIS at 254 nm..

A. Peak one was obtained as a colorless viscous oil, identified as (7bS,10aS)-3-acetyl-1,2,3,4,8,9,10,10a-Octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole.
Anal. Calcd. for $C_{16}H_{20}N_2O$ + .60 H_2O
Theory: %C, 71.93; %H, 8.00; %N, 10.49.
Found: %C, 72.06; %H, 7.79; %N, 10.73.
O.R.:[alpha]25/D=+118(19.2mg/mL) MeOH)

(7bS,10aS)-3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]-diazepino[6,7,1-hi]indole was treated with solid NaOH in MeOH under reflux to give (7bS,10aS)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino-[6,7,1-hi]-indole mp: 54-56 °C.
O.R.: [alpha]25/D=+134.18 (10.359mg/mL, MeOH)

B. Peak two was obtained as a colorless viscous oil, identified as (7bR,10aR)-3-acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole
Anal. Calcd. for $C_{16}H_{20}N_2O$ + .80 H_2O
Theory: %C, 70.98; %H, 8.04; %N, 10.35
Found: %C, 70.94; %H, 7.73; %N, 10.22
O.R.: [alpha]25/D=-132 (10.2mg/mL MeOH)

(7bR,10aR)-3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]-diazepino[6,7,1-hi]indole was treated with solid NaOH in MeOH under reflux to give 7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]-indole mp: 57-59°C

Anal Calcd for $C_{14}H_{18}N_2$

Theory: %C,77.81; %H,8.49; %N, 12.96.

Found: %C,78.01; %H,8.64; %N, 12.90.

Example 5

(chiral salt resolution of 1,2,3,4,8,9,10,10a-Octahydro-7bH-cyclopenta[b][1,4]-diazepino[6,7,1-hi]indole)

(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]indole

The compound of Example 2 (10.0 g, 46.7 mmol) was dissolved in isopropanol (500 mL) at 65-70°C under nitrogen and dibenzoyl-L-tartaric acid (4.18 g, 11.7 mmol) was added all at one time. The resultant solids were slurried at 70-75°C for two h, cooled to room temperature and stored at 10°C for 12 h. The solids were filtered and washed twice with isopropanol (15 mL). The solids were reslurried in hot (80°C) isopropanol (400 mL) for 1.5 h, cooled to room temperature and stored at 10°C for 12 h. The solids were filtered and washed twice with isopropanol (15 mL) and air dried to give 7.3g (79.9%) of the dibenzoyl-L-tartaric acid salt of the title compound as a white solid, mp: 163-5°C.

Anal. Calcd for $C_{14}H_{18}N_2 \cdot 0.5\ C_{18}H_{14}O_8 \cdot 0.4\ C_3H_8O$

Calcd: %C, 69.60; %H, 6.75; %N, 6.70.

Found: %C, 69.80; %H, 6.73; %N, 6.58.

O.R.: [alpha]25/D=-138.4 (1 mg/mL, MeOH)

The above tartrate salt (9.5 g, 12.1 mmol) was slurried in ethyl acetate (950 mL) and 1 N hydrochloric acid was added (25.0 mL, 25.0 mmol). The slurry was concentrated by atmospheric distillation (72-77°C) to a volume of 275 mL, cooled to room temperature and stored overnight at 10°C. The solids were filtered and washed twice with ethyl acetate (20 mL) and air dried to give 5.7 g (92.8 %) of the hydrochloride salt of the title compound as a white solid, mp 246-249 °C decomposed.

The HCl salt (5.6 g) was dissolved in ethanol (100 mL) at reflux. Upon cooling to room temperature, needle-like crystals formed. The mixture was stored overnight at 10°C. The solids were filtered, washed twice with ethanol (10 mL) and vacuum dried (57 °C /0.1mm) to give 3.8 g (67.8 %) of white solid, mp 252-253 °C decomposed.

Anal. Calcd for $C_{14}H_{18}N_2 \cdot HCl$

Calcd: %C, 67.05; %H, 7.64; %N, 11.17.

Found: %C, 66.74; %H, 7.54; %N, 11.09.

Example 6

6-Methyl-1,2,3,4,9,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

By the same procedure as described for Example 1, 4-acetyl-7-methyl-2,3,4,5-tetrahydro-1,4-benzodiazepine, (3.64 g ,17.8 mmol) was converted to 246 mg of the title compound as a white solid, mp: 168-170°C

Anal. Calcd for $C_{15}H_{18}N_2 \cdot 0.1\ H_2O$

Calcd: %C, 78.98; %H, 8.04; %N, 12.28.

Found: %C, 78.87; %H, 8.15; %N, 12.04.

Example 7

(2*S*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta-[*b*][1,4]Diazepino[6,7,1-*hi*]Indole

A. 1,2,3,4-Tetrahydrocyclopenta[*b*]Indole-5-Carboxylic Acid

To a stirred solution of 2-hydrazinobenzoic acid hydrochloride (53 mmol, 10.0 g) and cyclopentanone (58 mmol, 4.9 g) in 1,4-dioxane (100 mL) was added dropwise concentrated H_2SO_4 (~18M, 63 mmol, 3.5 mL). The resulting solution was heated to reflux for 2 hours. ^1H NMR analysis of a crude aliquot indicated complete reaction. The reaction was allowed to cool to room temperature and then concentrated to dryness to give a red solid which was used without further purification.

^1H NMR (DMSO-d_6, 300MHz) δ 10.8(s, 1H), 7.6-7.0(m, 3H), 2.8(m, 4H), 2.4(m, 2H).

B. Ethyl (2*S*)-2-[(1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoate

To a stirred, cooled (0°C) solution of crude 1,2,3,4-tetrahydrocyclopenta[*b*]-indole-5-carboxylic acid (60 mmol, 12 g), L-alanine ethyl ester (72 mmol, 11 g), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (72 mmol, 14 g), 1-hydroxybenzotriazole (HOBT) (72 mmol, 10 g) in CH_2Cl_2 (100 mL) was slowly added diisopropylethylamine (360 mmol, 46 g). The reaction mixture was stirred overnight while warming to room temperature. The reaction was concentrated *in vacuo* and the resulting oil was partitioned between water and ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated to a brown oil. The crude material was purified by chromatography through silica gel (Biotage) eluting with 15% ethyl acetate-hexanes to afford a yellow oil (8.4 mmol, 2.5 g, 16% yield over 2 steps).

^{1}H NMR (DMSO-d_6, 300MHz) δ 10.9(s, 1H), 8.74(d, 1H), 7.62(d, 1H), 7.48(d, 1H), 6.98(t, 1H), 4.47(t, 1H), 4.08(m, 2H), 2.75(m, 4H), 2.40(m, 2H), 1.42(d, 3H), 1.15(t, 3H).

C. Ethyl (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)-Amino]Propanoate

A solution of ethyl (2*S*)-2-[(1,2,3,4-tetrahydrocyclopenta[*b*]indol-5-ylcarbonyl)-amino]propanoate (8.4 mmol, 2.5 g) in ethanol (40 mL) was added to a mixture of 5% palladium on carbon (2 g) in ethanol (20mL). Concentrated hydrochloric acid (10 mL) was added and the resulting mixture was hydrogenated at 45 psi for 4 hours. The reaction mixture was filtered through Celite. The filter bed was washed well with ethanol and the combined filtrates were concentrated. The resulting oil was partitioned between 1 N NaOH and ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and concentrated to yield an oil (1.9 g, 6.1 mmol, 73% yield).
^{1}H NMR (DMSO-d_6, 300MHz) δ 8.7(m, 1H), 7.63(m, 1H), 7.25(m, 1H), 6.85(m, 2H), 4.40(m, 2H), 4.10(m, 2H), 3.76(m, 1H), 1.90(m, 2H), 1.68(m, 3H), 1.38(d, 3H), 1.31(m, 1H), 1.16(t, 3H).

D. (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoic Acid

A 1 M aqueous lithium hydroxide solution (13 mmol, 13 mL) was added to a solution of ethyl (2*S*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-ylcarbonyl)-amino]propanoate (6.1 mmol, 1.9 g) in THF (50 mL). The reaction mixture was stirred at room temperature for 18 h. The reaction was concentrated *in vacuo* and diluted with 0.1 N HCl and ethyl acetate. The phases were separated and the organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil (1.6 g, 6.1 mmol, quantitative yield).

^{1}H NMR (DMSO-d_6, 300MHz) δ 12.4(s, 1H), 8.21(d, 1H), 7.43(m, 1H), 7.01(d, 1H), 6.70(br s, 1H), 6.40(t, 1H), 4.35(m, 2H), 3.63(t, 1H), 1.88(m, 2H), 1.62(m, 4H), 1.30(d, 3H).

E. (2*S*)-2-Methyl-2,3,8,9,10,10a-Hexahydro-7b*H*-Cyclopenta[*b*][1,4]Diazepino-[6,7,1-*hi*]Indole-1,4-Dione

A solution of (2*S*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-yl-carbonyl)amino]propanoic acid (6.1 mmol, 1.6 g) was dissolved in acetic acid (50 mL) and heated to reflux for 18 h. The reaction was allowed to cool to room temperature and was concentrated to dryness. The crude material was purified by flash column chromatography (silica gel; 1:1 ethyl acetate-hexanes) to provide two diastereomers: less polar product (0.88 mmol, 0.23 g, 14%) and more polar product (0.18 mmol, 45 mg, 3%). The mixed fractions were also collected to provide another 3.9 mmol (1.0 g, 64%) of material.

Less Polar Product (A)

^{1}H NMR (DMSO-d_6, 300MHz) δ 8.2(d, 1H), 7.61(m, 1H), 7.46(dd, 1H), 7.16(t, 1H), 4.86(dt, 1H), 3.87(m, 2H), 1.92(m, 2H), 1.75(m, 1H), 1.58(m, 2H), 1.26(d, 3H), 1.06(m, 1H).

(2*S*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

A mixture of diastereomers of (2*S*)-2-methyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (3.9 mmol, 1.0 g) was suspended in 1 M BH_3•THF (15 mL) and heated to reflux for 18 h. After cooling to room temperature, the solution was quenched with methanol and concentrated. The resulting solid was suspended in 1 N NaOH and stirred at room temperature for 1 h. The aqueous phase was then extracted with chloroform and the combined extracts were

dried over $MgSO_4$, filtered, and concentrated to give a yellow solid (3.5 mmol, 0.80 g, 90%). Flash chromatography through silica gel (gradient elution 5%-10% methanol-chloroform) afforded the two diastereomers. The less polar product was arbitrarily assigned the *R,R* configuration and the more polar product the *S,S* configuration.

Anal. Calcd. for $C_{15}H_{20}N_2 \cdot 1.5mol\ H_2O$: C, 70.56; H, 9.08; N, 10.97.
Found: C, 70.24; H, 9.58; N, 10.81.
MS ((+))APCI, m/e (%)) 229(100, $[M+H]^+$).
IR (solid ATR, cm^{-1}) 2960, 2880, 2310, 1460, 1440, 1210, 1160, 1120, 1090, 1070.
^1H NMR (DMSO-d_6, 400MHz) δ 7.32(t, J=7.56Hz, 1H), 7.22(d, J=7.3Hz, 1H), 7.12(d, J=7.3Hz, 1H), 4.35(m, 1H), 4.07(m, 2H), 3.82(d, J=16.84Hz, 1H), 3.62(m, 1H), 3.14(dd, J=8.54Hz, 10.74Hz, 1H), 3.0(m, 1H), 2.04-1.69(m, 4H), 1.51(m, 2H), 1.22(d, J=6.6Hz, 4H).
$[\alpha]_D$ +99 (c. 0.11, DMSO).

Example 8

(2*S*)-(*rel*-7b*S*,10a*S*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

Following the procedure of method 7F, the more polar material provided the product which was assigned the *S,S* configuration.
Anal. Calcd. for $C_{15}H_{20}N_2 \cdot 1.1mol\ H_2O$: C, 72.60; H, 9.02; N, 11.29.
Found: C, 72.63; H, 8.80; N, 10.95.
MS ((+)APCI, m/e (%)) 229(100, $[M+H]^+$).
^1H NMR (DMSO-d_6, 400MHz) δ 6.86(d, J=7.3Hz, 1H), 6.73(d, J=7.3Hz, 1H), 6.52(t, J=7.4Hz, 1H), 3.95(m, 2H), 3.82(d, J=15.86Hz, 1H), 3.61(m, 1H), 3.41(dd, J=3.17Hz, 13.4Hz, 2H), 3.21(m, 1H), 2.83(dd, J=3.9Hz, 13.2Hz, 1H), 1.94(m, 1H), 1.77(m, 1H), 1.55(m, 4H), 1.15(d, J=6.6Hz, 3H).
$[\alpha]_D$ +38 (c. 0.10, DMSO).

Example 9

(2*R*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

A. **Methyl (2*R*)-2-[(1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoate**

Following the procedure of method 7B, employing D-alanine methyl ester (64 mmol, 8.9 g) afforded a yellow oil (4.9 mmol, 1.4 g).

^{1}H NMR (DMSO-d_6, 300MHz) δ 10.8(s, 1H), 8.78(d, 1H), 7.61(d, 1H), 7.49(d, 1H), 7.0(t, 1H), 4.5(m, 1H), 3.63(s, 3H), 2.76(m, 4H), 2.42(m, 2H), 1.42(d, 3H).

B. **Methyl (2*R*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)-Amino]Propanoate**

Following the procedure of method 7C, methyl (2*R*)-2-[(1,2,3,4-tetrahydrocyclopenta-[*b*]indol-5-ylcarbonyl)amino]propanoate (4.9 mmol, 1.4 g) was hydrogenated using 5% Pd/C (1.5 g) and concentrated HCl (7 mL) in methanol (25 mL) to yield an oil (2.7 mmol, 0.77 g, 55%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 8.34(d, 1H), 7.44(d, 1H), 7.02(d, 1H), 6.70(s, 1H), 6.41(t, 1H), 4.39(m, 2H), 3.65(m, 1H), 3.60(s,3H), 1.89(m, 1H), 1.61(m, 4H), 1.35(d, 3H), 1.29(m, 1H).

C. **(2*R*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoic Acid**

Following the procedure of method 7D, methyl (2*R*)-2-[(1,2,3,3a,4,8b-hexa-hydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]propanoate (2.7 mmol, 0.77 g) was

hydrolyzed to the acid using 1 M aqueous lithium hydroxide (5.9 mL) in THF (20 mL) to yield an orange oil which was used directly in the next step.

^{1}H NMR (DMSO-d_6, 300MHz) δ 12.4(br s, 1H), 8.2(d, 1H), 7.43(d, 1H), 7.01(d, 1H), 6.9(br s, 1H), 6.4(t, 1H), 4.33(m, 2H), 3.62(t, 1H), 1.89(m, 2H), 1.61(m, 4H), 1.32(d, 3H).

D. **(2*R*)-2-Methyl-2,3,8,9,10,10a-Hexahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino-[6,7,1-*hi*]Indole-1,4-Dione**

Following the procedure of method 7E, (2*R*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]propanoic acid was cyclized by refluxing in acetic acid (50 mL). Purification by flash chromatography through silica gel (elution with 5% methanol-chloroform) provided each diastereomer: less polar product (1.5 mmol, 0.39 g, 56% over 2 steps) arbitrarily assigned as the *R,R* configuration and more polar product (0.47 mmol, 0.11 g, 17% over 2 steps) assigned as the *S,S* configuration.

Less Polar Product (A)

^{1}H NMR (DMSO-d_6, 300MHz) δ 8.2(d, 1H), 7.62(d, 1H), 7.46(d, 1H), 7.16(t, 1H), 4.87(m, 1H), 3.88(m, 2H), 1.94(m, 3H), 1.76(m, 1H), 1.59(m, 2H), 1.28(d, 3H).

E. **(2*R*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta-[*b*][1,4]Diazepino[6,7,1-*hi*]Indole**

Following the procedure of method 7F, (2*R*)-(*rel*-7b*R*,10a*R*)-2-methyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*]-[1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (1.5 mmol, 0.39 g) was reduced with 1 M BH_3•THF (10 mL) to yield a yellow solid (0.47 mmol, 0.11 g, 31%).

Anal. Calcd. for $C_{15}H_{20}N_2$ • 0.15mol H_2O: C, 77.98; H, 8.86; N, 12.12.

Found: C, 77.72; H, 9.03; N, 11.89.

MS ((+)ESI, m/e(%)) 457(17, $[2M+H]^+$), 307(81, $[M+H+DMSO]^+$), 229(100, $[M+H]^+$).

IR (solid ATR, cm^{-1}) 3240, 2950, 2870, 1590, 1460, 1350, 1290, 1270, 740.
^1H NMR (DMSO-d_6, 400MHz) δ 6.8(d, J=7.1Hz, 1H), 6.65(d, J=7.1Hz, 1H), 6.47(t, J=7.3Hz, 1H), 3.94(m, 1H), 3.80, 3.71(ABq, J_{AB}=16.1Hz, 2H), 3.59(m, 1H), 3.35(dd, J=3.17Hz, 12.93Hz, 1H), 3.02(m, 1H), 2.75(dd, J=4.39Hz, 12.93Hz, 1H), 2.49(m, 1H), 1.94(m, 1H), 1.76(m, 1H), 1.56(m, 4H), 1.07(d, J=6.6Hz, 3H).
$[\alpha]_D$ -82 (c. 0.10, DMSO).

Example 10

(2*R*)-(*rel*-7b*S*,10a*S*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

Following the procedure of method 7F, (2*R*)-(*rel*-7b*S*,10a*S*)-2-methyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*]-[1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (0.47 mmol, 0.11 g) was reduced with 1 M BH_3•THF (8 mL) to yield the product (0.27 mmol, 61 mg, 57%).
MS ((+)APCI, m/e (%)) 457(20, $[2M+H]^+$), 229(100, $[M+H]^+$).
^1H NMR (DMSO-d_6, 400MHz) δ 6.85(d, J=7.08Hz, 1H), 6.72(d, J=7.3Hz, 1H), 6.52(t, J=7.3Hz, 1H), 3.82(dd, J=5.6Hz, 9.0Hz, 1H), 3.79, 3.51(ABq, J_{AB}=15.1Hz, 2H), 3.70(dt, J=2.9Hz, 9.0Hz, 1H), 3.28(m, 1H), 3.06(dd, J=2.1Hz, 12.1Hz, 1H), 2.78(m, 1H), 2.43(m, 1H), 1.92-1.30(m, 6H), 1.02(d, J=6.6Hz, 3H).

Example 11

(2*R*,7b*S*,10a*S*)-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]Diazepino-[6,7,1-*hi*]Indol-2-ylmethanol

A. Methyl (2*S*)-3-Hydroxy-2-[(1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-yl-carbonyl)Amino]Propanoate

Following the procedure of method 7B, employing L-serine methyl ester (64 mmol, 9.9 g) afforded a yellow solid (8.9 mmol, 2.7 g, 14%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 10.8(s, 1H), 8.51(d, 1H), 7.61(d, 1H), 7.51(d, 1H), 7.01(t, 1H), 5.08(m, 1H), 4.56(q, 1H), 3.82(d, 2H), 3.62(s, 3H), 2.76(m, 4H), 2.42(m, 2H).

B. Methyl (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)-Amino]-3-Hydroxypropanoate

Following the procedure of method 7C, methyl (2*S*)-3-hydroxy-2-[(1,2,3,4-tetrahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]propanoate (8.9 mmol, 2.7 g) was hydrogenated using 5% Pd/C (2 g) and concentrated HCl (10 mL) in methanol (25 mL) to yield the crude product (8.9 mmol, 2.7 g, quantitative).
^{1}H NMR (DMSO-d_6, 300MHz) δ 8.3(d, 1H), 7.86(d, 1H), 7.34(d, 1H), 7.03(t, 1H), 5.80(br s, 2H), 4.45(m, 2H), 3.80(m, 2H), 3.61(s, 3H), 2.0-1.55(m, 6H).

C. (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl]Amino}-3-Hydroxypropanoic Acid

Following the procedure of method 7D, methyl (2*S*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]-3-hydroxypropanoate (8.9 mmol, 2.7 g) was hydrolyzed to the acid using 1 M aqueous lithium hydroxide (40 mL) in THF (40 mL) to yield a red oil (1.5 mmol, 430 mg, 17%).
^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.92(d, 1H), 7.40(d, 1H), 7.03(d, 1H), 6.43(t, 1H), 4.39(m, 2H), 3.63(br m, 4H), 2.0-1.2(m, 6H).

D. (2*S*)-2-(Hydroxymethyl)-2,3,8,9,10,10a-Hexahydro-7b*H*-Cyclopenta[*b*]-[1,4]-Diazepino[6,7,1-*hi*]Indole-1,4-Dione

Following the procedure of method 7E, (2*S*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]-3-hydroxypropanoic acid (1.5 mmol, 430 mg) was cyclized by refluxing in acetic acid (40 mL). Purification by flash chromatography

through silica gel (elution with 5% methanol-chloroform) provided each diastereomer: less polar product (0.55 mmol, 0.15 g, 37%) arbitrarily assigned as the *R,R* configuration and more polar product (0.26 mmol, 0.070 g, 17%) assigned as the *S,S* configuration.

Less Polar Product (A)

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.44(d, 1H), 7.63(d, 1H), 7.48(d, 1H), 7.19(m, 1H), 4.88(m, 1H), 4.39(dd, 1H), 4.22(t, 1H), 4.07(m, 1H), 3.91(m, 1H), 2.0-1.5(m, 6H).

E. (2*R*)-(*rel*-7b*S*,10a*S*)-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]-Diazepino[6,7,1-*hi*]Indol-2-ylmethanol

Following the procedure of method 7F, (2*S*)-(*rel*-7b*S*,10a*S*)-2-hydroxymethyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*]-[1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (0.26 mmol, 0.070 g) was reduced with 1 M BH_3•THF (1 mL) to yield a solid (0.17 mmol, 0.046 g, 65%).

MS ((+)APCI, m/e(%)) 323(35, $[M+H+DMSO]^+$, 245(100, $[M+H]^+$).

^{1}H NMR (DMSO-d_6, 400MHz) δ 6.85(d, J=7.1Hz, 1H), 6.73(d, J=7.3Hz, 1H), 6.52(t, J=7.3Hz, 1H), 4.70(m, 1H), 3.86, 3.50(ABq, J_{AB}=14.9Hz, 2H), 3.85(m, 1H), 3.70(dt, J=2.9Hz, 9.0Hz, 1H), 3.35(m, 1H), 3.22(m, 2H), 2.64(m, 1H), 2.40(m, 1H), 1.90(m, 1H), 1.75(m, 1H), 1.60(m, 2H), 1.50(m, 1H), 1.40(m, 2H).

Example 12

rel-(4*S*,7b*S*,10a*S*)-4-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]-Diazepino[6,7,1-*hi*]Indole

A. 1,2,3,4-Tetrahydrocyclopenta[*b*]Indole

Concentrated sulfuric acid (~18 M, 35 mL) was added dropwise to a mixture of phenyl hydrazine (510 mmol, 50 mL) and cyclopentanone (45 mL, 510 mmol) in water

(250 mL). The resulting mixture was heated to reflux for 30 min and then allowed to cool to room temperature. The liquid was decanted from the reaction mixture leaving a red, gummy solid. Hexanes (500-600 mL) was added to the flask and the mixture was heated to reflux. The yellow hexane solution was decanted hot from the mixture and placed in the freezer (crystallization begins immediately). More hexanes is added to the flask and the procedure repeated two more times using a total volume of 1500 mL of hexanes. After 1 h in the freezer, the solid was collected from the flasks and dried providing the known indole (410 mmol, 65 g, 80%).

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91

Found: C, 83.92; H, 7.12; N, 8.85

B. 1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indole

A mixture of 1,2,3,4-tetrahydrocyclopenta[*b*]indole (11 mmol, 1.8 g), 5% Pd/C (0.5 g), and concentrated hydrochloric acid (1.2 mL) was hydrogenated at 45 psi on a Parr shaker. After 3 h, the mixture was removed from the shaker and filtered through Celite. The solid bed was washed with methanol. The filtrate was concentrated. The crude oil was dissolved in 1 N HCl and washed with ether. The aqueous phase was treated with 2.5 N NaOH to pH >10 and then extracted with chloroform. The combined chloroform extracts were dried over $MgSO_4$, filtered and concentrated to give the crude indoline. The material was purified by flash column chromatography through silica gel (Biotage, elution with 10% ethyl acetate-hexanes) to give the known indoline (7.6 mmol, 1.2 g, 69%) as a clear oil.

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80

Found: C, 82.61; H, 8.35; N, 8.72

C. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]Indol-4(1*H*)-yl)Acetamide

To a stirred solution of 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (130 mmol, 21 g) in DMF (50 mL) was added diisopropylethylamine (400 mmol, 70 mL) followed

by 2-chloroacetamide (270 mmol, 25 g). The reaction mixture was heated to 100°C for 18 h. The reaction was concentrated and the diluted with ethyl acetate and water. The phases were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash column chromatography through silica gel (elution with 60% ethyl acetate-hexanes) to afford a yellow solid (90 mmol, 20 g, 69%).

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95.

Found: C, 72.45; H, 7.57; N, 12.64.

MS ((+)APCI, m/e(%)) 217(100, $[M+H]^+$).

IR (solid ATR, cm^{-1}) 3450, 2930, 2870, 1680, 1480, 1150, 740.

^1H NMR (DMSO-d_6, 400MHz) δ 7.20(s, 1H), 7.05(s, 1H), 6.90(m, 2H), 6.48(dt, J=0.73Hz, 7.3Hz, 1H), 6.18(d, J=7.8Hz, 1H), 4.22(m, 1H), 3.70, 3.58(ABq, J_{AB}=17.1Hz, 2H), 3.64(m, 1H), 1.90(m, 1H), 1.78(m, 1H), 1.56(m, 3H), 1.40(m, 1H).

D. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]Indol-4(1*H*)-yl)Ethylamine

2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]i ndol-4(1*H*)-yl)acetamide (90 mmol, 20 g) was dissolved in 1 M BH_3•THF (200 mL) and heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature and then quenched slowly with methanol. The solution was concentrated, dissolved in methanol, and again concentrated. The resulting oil was diluted with ether and extracted twice with 1 N HCl. The aqueous phase was treated with 2.5 N NaOH to pH >10 and extracted with chloroform. The combined chloroform extracts were dried over $MgSO_4$, filtered and concentrated to provide a yellow oil which was used without further purification.

Anal. Calcd. for $C_{13}H_{18}N_2$ • 0.55mol H_2O: C, 73.58; H, 9.07; N, 13.20.

Found: C, 73.62; H, 8.80; N, 12.83.

MS (EI, m/e(%)) 202(10, M^+), 172(100), 130(20).

IR (film ATR, cm^{-1}) 2950, 2870, 1605, 1480, 1250(br), 730.

^{1}H NMR (DMSO-d_6, 400MHz) δ 6.89(dd, J=0.73Hz, 7.3Hz, 2H), 6.42(dt, J=0.73Hz, 7.3Hz, 1H), 6.29(d, J=7.6Hz, 1H), 4.12(m, 1H), 3.62(dt, J=2.4Hz, 9.0Hz, 1H), 3.08(m, 2H), 2.65(m, 2H), 1.90(m, 1H), 1.75(m, 1H), 1.58(m, 3H), 1.43(m, 1H).

E. *rel*-(4*S*,7b*S*,10a*S*)-4-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

2-(2,3,3a,8b-tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)ethylamine (4.9 mmol, 1.0 g) was dissolved in ethanol (25 mL) at room temperature and trifluoroacetic acid (4.9 mmol, 380 μL) was added, followed by acetaldehyde (4.9 mmol, 280 μL). The reaction was heated to reflux overnight. The reaction vessel was cooled and then concentrated *in vacuo*. The resulting oil was partitioned between $CHCl_3$ and 1N NaOH. The aqueous phase was extracted again with $CHCl_3$. The combined organics were washed with 1N NaOH, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a brown oil (23.8 mmol). The crude product was purified by flash chromatography (SiO_2) eluting with 10%MeOH/$CHCl_3$ to give the two racemic diastereomers.

Less Polar Product:

Rf 0.5 (A) 10%Et_3N/EtOAc

MS ((+)APCI, m/e(%)) 229(100, $[M+H]^+$).

IR (film ATR, cm^{-1}) 2940, 2860, 1600, 1460, 1430, 1330, 1300, 1230, 1070, 750.

^{1}H NMR (DMSO-d_6, 400MHz) δ 6.88(d, J=7.3Hz, 1H), 6.81(d, J=7.8Hz, 1H), 6.59(t, J=7.4Hz, 1H), 3.87(m, 1H), 3.71(m, 1H), 3.45(q, J=6.7Hz, 1H), 3.06(m, 2H), 2.80-2.67(m, 2H), 2.05(br m, 1H), 1.90(m, 1H), 1.75(m, 1H), 1.64(m, 1H), 1.52(m, 2H), 1.37 (m, 1H), 1.37(d, J=6.8Hz, 3H).

Example 13

***rel*-(4*R*,7b*S*,10a*S*)-4-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]Diazepino[6,7,1-*hi*]Indole**

The title product was prepared in Example 12E isolating the more polar product.

Rf 0.39 (B) 10%Et_3N/EtOAc

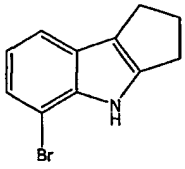
MS ((+)APCI, m/e(%)) 229(100, $[M+H]^+$).

IR (film ATR, cm^{-1}) 2950, 2930, 2860, 1600, 1460, 1430, 1320, 1230, 1050, 750.

^1H NMR (DMSO-d_6, 400MHz) δ6.81(d, J=7.1Hz, 1H), 6.71(d, J=7.6Hz, 1H), 6.52(t, J=7.3Hz, 1H), 4.0(q, J=6.9Hz, 1H), 3.82(dd, J=4.7Hz, 8.6Hz, 1H), 3.68(dt, J=2.7Hz, 8.9Hz, 1H), 3.05(m, 2H), 2.82-2.70(m, 2H), 2.3(br m, 1H), 1.88(m, 1H), 1.78(m, 1H), 1.64-1.48(m, 3H), 1.40(m, 1H), 1.17(d, J=7.1Hz, 3H).

Example 14

Fisher Indole Synthesis of 5-Bromo-1,2,3,4-Tetrahydrocyclopenta[*b*]Indole:



A mixture of 2-bromophenylhydrazine hydrochloride (130 g, 0.582 mol) and cyclopentanone (60 mL, 0.678 mol) in 4% sulfuric acid (1 L) was heated to 98-100°C for 6 h. This was then allowed to cool to rt overnight. After 12 h, the liquid was decanted leaving a red, gummy solid. (5:1) Hexane:EtOAc (1.5 L) was added to the flask and the mixture was hot filtered. The organic layer was concentrated *in vacuo* to give a brown oil which solidified upon standing to give 77.4 g (59%) of a brown solid.

R_f = 0.54 (hexane:EtOAc);

^1H NMR ($CDCl_3$) δ 8.12 (d, J=8.6 Hz, 1H), 7.76 (m, 2H), 7.51 (d, J=9 Hz, 1H), 7.20-7.60 (m, 4H), 4.5-4.6 (m, 1H), 4.2-4.4 (m, 3H), 4.1-4.2 (m, 1H), 2.70 (s, 3H), 2.39 (s, 3H);

^{13}C NMR (DMSO) δ 144.8, 139.6, 126.4, 123.2, 121.4, 121.0, 118.1, 104.9, 29.0, 26.3, 25.0;

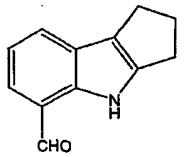
IR (KBr): υ_{max} 3436, 2941, 2856, 1616, 1575, 1463, 1416, 1295, 1210, 1094, 768, 729, 629, 463 cm^{-1}.

Analysis for $C_{11}H_{10}BrN$: Calculated: C 55.91 H 4.24 N 5.93

Found: C 57.13 H 4.22 N 5.97

Example 15

Formylation to 1,2,3,4-Tetrahydrocyclopenta[*b*]Indole-5-Carbaldehyde:



A solution of 5-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indole (15.5 g, 65.1 mmol) in MTBE (130 mL) was cooled to 0-5°C in an ice-bath before *n*-BuLi in hexanes (2.5 M, 57.5 mL, 144 mmol) was added slowly while keeping the reaction mixture below 20°C. After 30 min, DMF (50.5 mL, 0.652 mmol) was added slowly. Some solid precipitate formed upon addition. This was stirred under these conditions for an additional 1 h then the ice-bath was removed to allowed the reaction mixture to warm to rt. MTBE (130 mL) and water (100 mL) were added. The two layer were separated. The aqueous layer was extracted with MTBE (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 15.4 g (127%) of crude product as a light brown solid.

R_f = 0.41 (5:1 hexane:EtOAc);

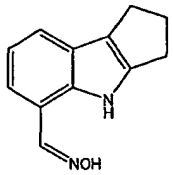
^{1}H NMR ($CDCl_3$) δ 10.1 (s, 1H), 9.9 (bs, 1H), 7.71 (d, J=7.8 Hz, 1H), 7.52 (d, J=7.4 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 2.7-3.0 (m, 4H), 2.4-2.6 (m, 2H);

^{13}C NMR ($CDCl_3$) δ 193.7, 146.0, 138.5, 127.1, 125.7, 120.3, 119.7, 118.9, 28.8, 25.7, 24.2; GC/MS 185, 158, 128, 115, 102, 91, 77, 70, 63, 57, 51, 45, 39, 39;

IR (KBr): υ_{max} 3394, 2909, 2862, 2799, 2727, 1668, 1565, 1472, 1352, 1185, 1124, 780, 662 cm^{-1}.

Example 16

Preparation of 1,2,3,4-Tetrahydrocyclopenta[*b*]Indole-5-Carbaldehyde Oxime:



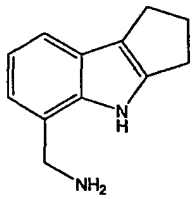
A mixture of 1,2,3,4-tetrahydrocyclopenta[*b*]indole-5-carbaldehyde (100 mg, 0.54 mmol) and hydroxylamine hydrochloride (60 mg, 0.86 mmol) in (2:1) pyridine:H_2O (4.5 mL) was stirred at room temperature. After 16 h, $CHCl_3$ (25 mL) and H_2O (15 mL) were added to the reaction mixture. The two layers were separated. The organic layer was extracted with 1 N HCl (2 x 10 mL), H_2O (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 117 mg (108%) of crude product as a brown oil.

R_f = 0.50 (20:1 $CHCl_3$:CH_3OH);

^1H NMR ($CDCl_3$) δ 9.50 (bs, 1H), 8.23 (s, 1H), 7.3-7.5 (m, 1H), 6.8-7.0 (m, 2H), 2.6-2.8 (m, 4H), 2.2-2.5 (m, 2H).

Example 17

Oxime Reduction to 1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-ylmethylamine:



A solution of 1,2,3,4-tetrahydrocyclopenta[*b*]indole-5-carbaldehyde oxime (1.6 g, 8.1 mmol) in THF (30 mL) was cooled to 0-5 °C in an ice-bath under Ar. LAH (0.93 g, 24.5 mmol) was added in small portions. After 2 h, the ice-bath was removed to warm the reaction mixture to rt over 16 h before a sat'd Na_2SO_4 solution (1.5 mL) was added dropwise to quench the excess reagent. After 30 min of stirring, solid Na_2SO_4 and Et_2O (30 mL) were added. The suspension was filtered and concentrated *in vacuo* to give 1.05 g (69%) of the title compound as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 9.3 (bs, 1H), 7.34 (d, J=7.8 Hz, 1H), 6.99 (t, J=7.5 Hz, 1H), 6.89 (d, J=7.1 Hz, 1H), 4.22 (s, 2H), 2.7-3.0 (m, 4H), 2.4-2.6 (m, 2H), 1.6 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 144.0, 140.0, 125.1, 125.2, 119.0, 118.9, 117.4, 45.3, 28.8, 25.9, 24.1; IR (KBr): υ_{max} 3417, 3352, 3289, 3055, 2897, 2849, 1615, 1582, 1419, 1325, 1229, 1129, 1000, 897, 741 cm^{-1}.

Analysis for $C_{12}H_{14}N_2$: Calculated: C 77.42 H 7.53 N 15.05

Found: C 74.60 H 7.31 N 13.52

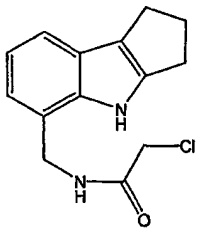
Example 18

One-Pot Reductive Amination to 1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-yl-methylamine:

A mixture of 1,2,3,4-tetrahydrocyclopenta[*b*]indole-5-carbaldehyde (578 mg, 3.12 mmol), hydroxylamine hydrochloride (238 mg, 3.42 mmol) and pyridine (3 mL) in THF (15 mL) was stirred at rt. After 5.5 h, the reaction mixture was cooled to 0-5°C in an ice-bath before LAH power (474 mg, 12.5 mmol) was added portionwise. The reaction mixture was then warmed to rt overnight before a sat'd Na_2SO_4 solution (1 mL) was added dropwise to quench the excess reagent. After 30 min of stirring, solid Na_2SO_4 and Et_2O (30 mL) were added. The suspension was filtered and concentrated *in vacuo* to give 338 mg (58%) of the title compound as a yellow solid.

Example 19

Acylation to 2-Chloro-N-(1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-ylmethyl)-Acetamide:



A solution of 1,2,3,4-tetrahydrocyclopenta[*b*]indol-5-ylmethylamine (100 mg, 0.538 mmol) and pyridine (0.1 mL, 1.23 mmol) in CH_2Cl_2 (2 mL) was cooled to 0-5°C

in an ice-bath under Ar before chloroacetyl chloride (62 μL, 0.59 mmol) was added. After 1 h, the ice-bath was removed to allow the reaction to warm to rt. After an additional 12 h, H_2O (3 mL) and $CHCl_3$ (3 mL) were added. The two layers were separated. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification on SiO_2, eluted with (40:1) $CHCl_3$:CH_3OH gave 80 mg (57%) of the title compound as a yellow solid.

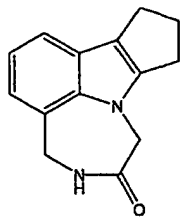
R_f= 0.52 (40:1 $CHCl_3$:CH_3OH);

^1H NMR ($CDCl_3$) δ 9.37 (bs, 1H), 7.41 (d, J=7.5 Hz, 1H), 7.16 (bs, 1H), 7.01 (t, J=7.3 Hz, 1H), 6.96 (d, J=7.8 Hz, 1H), 4.68 (d, J=6.8 Hz, 2H), 4.08 (s, 2H), 2.7-3.0 (m, 4H), 2.4-2.6 (m, 2H);

^{13}C NMR ($CDCl_3$) δ 167.6, 145.0, 139.8, 125.4, 121.4, 121.2, 120.9, 120.2, 119.4, 43.0, 41.9, 29.2, 26.4, 24.8.

Example 20

Seven-Membered Ring Closure to 3,4,9,10-Tetrahydro-8*H*-Cyclopenta[*b*][1,4]-Diazepino [6,7,1-*hi*]Indol-2(1*H*)-One:



To a suspension of NaH (124 mg, 3.10 mmol) in DMF (3 mL), 2-chloro-N-(1,2,3,4-tetrahydrocyclopenta[*b*]indol-5-ylmethyl)acetamide (135 mg, 0.515 mmol) in DMF (3 mL) was added at rt under Ar. After 16 h, H_2O (2 mL) was added to quench the excess reagent, H_2 evolved upon addition. After an additional 30 min, $CHCl_3$ (20 mL) and H_2O (10 mL) were added. The two layers were separated. The aqueous layer was extracted with $CHCl_3$ (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification on SiO_2, eluted with (30:1) $CHCl_3$:CH_3OH gave 67 mg (58%) of the title compound as a brown solid.

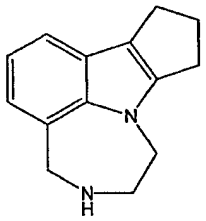
R_f= 0.53 (20:1 $CHCl_3$:CH_3OH);

^{1}H NMR ($CDCl_3$) δ 7.99 (bs, 1H), 7.33 (d, J=7.8 Hz, 1H), 6.95 (t, J=7.2 Hz, 1H), 6.75 (d, J=7.2 Hz, 1H), 4.87 (s, 2H), 4.56 (d, J=6.2 Hz, 2H), 2.7-3.0 (m, 4H), 2.4-2.6 (m, 2H);

^{13}C NMR ($CDCl_3$) δ 170.0, 146.6, 139.4, 125.1, 121.4, 119.6, 119.2, 118.8, 118.5, 51.3, 44.5, 28.7, 25.1, 25.0.

Example 21

Reduction to 3,4,9,10-Tetrahydro-8*H*-Cyclopenta[*b*][1,4]Diazepino [6,7,1-*hi*]-Indole:

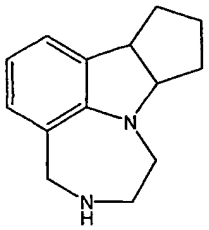


To a suspension of 3,4,9,10-tetrahydro-8*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indol-2(1*H*)-one (67 mg, 0.30 mmol) in Et_2O (7 mL), LAH power (28 mg, 0.74 mmol) was added slowly at rt under Ar. After 16 h, additional Et_2O (5 mL) was added followed by dropwise addition of a sat'd Na_2SO_4 solution (0.1 mL). H_2 gas evolved upon addition. Additional Et_2O (8 mL) was added, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 44 mg (70%) of the title compound as a yellow syrup.

^{1}H NMR ($CDCl_3$) δ 7.30 (d, J=7.7 Hz, 1H), 7.0 (t, J=7.5 Hz, 1H), 6.8 (d, J=7.1 Hz, 1H), 5.29 (s, 2H), 3.99 (t, J=5.1 Hz, 2H), 3.33 (t, J=5.0 Hz, 2H), 2.8-2.9 (m, 4H), 2.4-2.2.6 (m, 2H).

Example 22

Preparation of 1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]-Diazepino-[6,7,1-*hi*]Indole



To a solution of 3,4,9,10-tetrahydro-8*H*-cyclopenta[*b*][1,4]diazepino [6,7,1-*hi*]indole (61 mg, 0.29 mmol) in TFA (2 mL) being cooled in an ice-bath, BH_3.THF (0.7 mL, 0.7 mmol, 1 M THF) was added slowly under Ar. After 4 h, the reaction mixture was concentrated *in vacuo* then $CHCl_3$ (3 mL) and 1 N HCl (3 mL) were added. The mixture was stirred for 1 h before separating the two layers. The aqueous layer was basified to pH 13-14 with 5 N NaOH then extracted with $CHCl_3$ (3 x 3 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 36 mg (58%) of the title compound as a thin white film.

^{1}H NMR (DMSO-d_6) δ 6.86 (d, J=7.2 Hz, 1H), 6.74 (d, J=7.4 Hz, 1H), 6.53 (t, J=7.3 Hz, 1H), 3.88 (m, 1H), 3.81, 3.47 (ABq, J_{AB}=15.1 Hz, 2H), 3.73 (m, 1H), 3.08 (m, 2H), 2.55-2.80 (m, 2H), 2.15 (bs, 1H), 1.3-2.0 (m, 6H).

Example 23

1,2,3,4,9,10-Hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

To a suspension of benzodiazapine (92.0 g, 0.62 mole) and K_2CO_3 (90.2 g, 0.65 mole, -325 mesh) in CH_3CN (1000 ml) was added acetic anhydride (63.4 g, 58.6 ml, 0.62 mole) in 0.5 h (reaction mixture was cooled in ice water to maintain the reaction mixture temperature between 15-22 °C). The suspension was stirred for 0.5 h at room temperature (check TLC after 30min, eluent ethyl acetate:MeOH 9:1). The reaction mixture was evaporated and to the residue water (400 ml) was added. The suspension

was cooled in ice, filtered, washed with cold water (50 ml x 2). Dried under vacuum to give 109.7 g of 4-acetylbenzodiazepine as a white solid, yield 93%).

Preparation of Hydrazine (4-acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-1-ylamine

4-Acetylbenzodiazepine (28.5 g, 50.15 m) and allyl N-[(mesitylsulfonyl)-oxy]carbamate (53.8 g, 0.18 m) were combined in toluene (270 mL) and heated under reflux for 2.5 h. The reaction was quenched with 0.5 N NaOH. The precipitate that formed was removed by filtration and the aqueous filtrate was extracted with ethyl acetate (3X). The combined organic layers were washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give a residue which was dissolved in methylene chloride (490 mL) and treated with diethylamine (51 mL, 5 eq.) and tetrakis triphenylphosphinepalladium (115 mg, 0.001 eq). After stirring for 2 h at room temperature, the volatiles were removed under reduced pressure and the residue was purified by chromatography on silica gel eluting with 10-20% methanol in ethyl acetate to give 4-acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-1-ylamine (13.5 g, 44%) as a white solid.

Preparation of Hydrazone

4-Acetyl-N-cyclopentylidene-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-1-amine

4-Acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (30 g, 0.158 m) was dissolved in glacial acetic acid (287 mL). *Tert*-butylnitrite (20.6 mL) was added and the reaction mixture was stirred at room temperature. Meanwhile, a 2L round-bottomed flask was equipped with an mechanical overhead stirrer, nitrogen inlet tube, and a dropping funnel. Powdered zinc (32.8 g) was suspended in water (88 mL) with vigorous stirring. When a TLC (silica gel, 5%methanol in methylene chloride) indicated that all of the benzodiazepine had been converted to the nitroso compound, the zinc-water mixture was cooled in an ice bath and the nitroso solution was added

dropwise over 1.5 h with vigorous stirring. When all of the nitroso solution had been added, the ice bath was removed and stirring was continue for another 30 minutes. Cyclopentanone (41.8 mL) was added to the reaction vessel containing the hydrazine (generated *in situ*) which was then placed in a preheated oil bath and heated at 75-85°C (internal temperature.) Heating was continued until there was no more hydrazine as indicated by TLC on silica gel eluting with 10% methanol in ethyl acetate (2 h). After cooling to room temperature, the reaction mixture was diluted with methylene chloride (600 mL) and stirred at room temperature. The insoluble material was separated by filtration and washed with methylene chloride (3x 100 mL). The layers were combined and evaporated to give crude hydrazone, 64 g.

3-Acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

The crude hydrazone (64 g) was dissolved in 1-propanol (385 mL). *p*-Toluene-sulfonic acid hydrate (32 g) was added and the reaction vessel was placed in a pre-heated oil bath. The reaction mixture was heated under reflux for about 2.5 h (TLC analysis showed no hydrazone remaining). The heating bath was removed and the reaction mixture was stirred for an additional 15 minutes at room temperature. The reaction mixture was diluted with ethyl acetate (1200 mL) and cooled in an ice bath. 2.5 N NaOH was added with cooling and stirring until the aqueous phase remained basic (indicator paper, pH 12). The phases were separated and the organic phase was extracted with saturated sodium bicarbonate (2 x 300 mL). The aqueous phase was back extracted with one portion of ethyl acetate. The organic phases were combined, dried ($MgSO_4$), filtered and evaporated to give a dark brown residue. The residue was purified by column chromatography on silica gel eluting with 0.5-2% methanol in methylene chloride to give, 22.46 g (56%) of 3-acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole, as a viscous oil.

3-Acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole (2.34g , 9.20 mmol) was dissolved in MeOH . The solution was diluted with 2.5N

NaOH and solid NaOH pellets were added. The reaction mixture was placed in an oil bath at 95 °C for 6 h. then cooled to room temperature and stirred overnight. The volatiles were evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The ethyl acetate was separated and evaporated and the residue was dissolved in methylene chloride and purified by chromatography on silica gel eluting with 2-5% methanol in methylene chloride to give the product of Example 23 as a light grey solid 1.56g (80%) , mp: 66-68 °C.

Anal. Calcd. for $C_{14}H_{16}N_2$

Theory: %C, 79.21; %H, 7.60; %N, 13.20.

Found: %C, 78.81; %H, 7.5 ; %N, 13.10

Example 24

1,2,3,4,8,9,10,10a-Octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

Method A.

The compound of Example 23 (1.56g, 7.35 mmol) was dissolved in trifluoroacetic acid (53 mL) and cooled in an ice/water bath. 1.5 M BH_3 in THF (34 mL) was added dropwise slowly and stirred for an additional 15min. After the addition was complete, water was added slowly to quench the reaction. This was followed by 2.5 N NaOH and 50% NaOH until the reaction mixture was basic (yellow color disappeared). After extraction with ethyl acetate (3X), the organic phases were combined and concentrated under reduced pressure to give a residue which was purified by chromatography on silica gel eluting with 3-10% MeOH in methylene chloride to give 600mg (38%) of the product as a yellow solid: mp 64-68°C.

Anal. Calcd for $C_{14}H_{18}N_2 \cdot 0.2\ H_2O$

Calcd: %C, 77.17; %H, 8.51; %N, 12.86.

Found: %C, 77.13; %H, 8.18; %N, 12.61.

Method B.

4-Acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-1-carboxamide

To a solution of 4-acetylbenzodiazepine (20.0g, 0.105 mole) in acetonitrile (100 ml) at room temperature was added sodium cyanate (27.4g, 0.42 mole). The resulting suspension was heated to 50°C and then trifluoroacetic acid (24.0 g, 0.21 mole) was added slowly dropwise over 30 min. Heating was continued at 50°C for 1h. The reaction mixture was cooled to room temperature and the solvent was evaporated to give a white residue. Water (160 ml) was added to the residue and the mixture was cooled in ice for 1h. The solids were collected by filtration and washed with cold water. After drying under house vacuum 23.6 g (96%) of product was obtained as a white solid.

NMR (300 MHz, DMSO): δ 7.2-7.5 (4H, m), 5.76 (2H, br.s), 4.46 (2H, br.s), 3.61 (2H, br.s), 2.0 (3H, two singlets).

GC-MS: 98%.

HPLC purity (area %): 97.4%

LC-MS: 96.7%.

4-Acetyl-N-cyclopentylidene-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-1-amine

To a mixture of ethanol (95 ml) and water (95 ml) was added sodium hydroxide pellets (11.5g, 0.288 mole). The mixture was cooled in an ice bath and then 4-acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-1-carboxamide (19.2g, 0.082 mole) was added. To the milky suspension at 4°C was added sodium hypochlorite (94.0 ml, 0.164 mole, 10-13%) over 10 min. The reaction mixture was warmed to ambient temperature. A clear solution was observed. After 2h, the reaction mixture was cooled in an ice bath and acetic acid (82.0 ml) was added. To this solution cyclopentanone (8.3g, 0.988 mole) was added. After 1.5h at room temperature the reaction mixture was cooled in an ice bath and neutralized with 10 N sodium hydroxide. The aqueous phase was extracted with ethyl acetate (125 ml, 50 ml x 2) and the combined organic layers

were washed with brine (200 ml), dried (Na_2SO_4) and evaporated to give a syrup, 17.8g (yield 80%) of the hydrazone product. The crude hydrazone was used without purification in the Fischer-Indole cyclization.

LC-MS: 93%.
GC-MS: 94%.

3-Acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole

To a gummy amber colored hydrazone (0.78 g of 94% pure by GC) was added a solution of 4% aq.H_2SO_4 (5 ml H_2O + 0.2 ml Conc.H_2SO_4). The clear reaction mixture solution was heated to reflux for 1h. After cooling the reaction mixture, it was extracted with ethyl acetate. The ethyl acetate layer was washed with 5% $NaHCO_3$ solution and saturated sodium chloride solution and dried ($MgSO_4$). Filtration and evaporation of the volatiles from the filtrate gave 0.48 g of 3-acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole
as an off-white solid (66%).

NMR (300 MHz, DMSO): δ 7.22 (1H, m), 6.8 (2H, m), 4.85 (2H, two singlets), 4.18 (2H, m), 3.98 (2H, m) 2.7 (4H, m), 2.46 (2H, m), 2.04 (3H, two singlets).

GC-MS: 98%.

To 5%Pd/C (3.5g) was added ethanol (360 ml), 3-acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole (35.8g, 0.141 mole) and conc.HCl (13.9 ml, 0.141 mole). The suspension was hydrogenated in a Parr apparatus at 35 psi. for 4h. The reaction mixture was filtered through Celite, washed with ethanol (100 ml x 2) and evaporated to give 46.4 g of crude 3-acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole hydrochloride salt, which was used as such in the next step.

To a flask fitted with a reflux condenser, was added KOH (79.4g), MeOH (136 ml) and water (36 ml). When KOH was dissolving the reaction mixture exothermed to reflux, then it became a clear solution (Claisen alkali). The above solution (warm or hot) was added to the fused indoline (46.4g) and the resulting suspension was refluxed for 15 h. On cooling the reaction mixture to room temperature 1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole crystallized out of the reaction mixture. The solids were collected by filtration and washed with water (50 ml x 4). The wet product (28.8 g) was slurried in water (300 ml) at room temperature for 30 min, filtered, washed with water (30 ml x 6) and dried under house vacuum at 40 °C for 6 h to give 26.72g (88.6% over two steps: reduction and deprotection) of the product of Example 24.

HPLC: (97.89% area)
NMR (300 MHz, DMSO): δ 6.86 (1H, d, J=7.2Hz), 6.74 (1H, d, J=7.3Hz), 6.53 (2H, t, J=7.3Hz), 3.9 (1H, br.t), 3.81 (1H, d, J=15Hz), 3.48 (1H, d, J=15Hz), 3.04-3.15 (2H, m), 2.2 (1H, br.s), 1.85-2.0 (1H, m), 1.73-1.84 (1H, m), 1.34-1.72 (4H, m).
GC-MS: 99.9%.

Example 25

3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]-indole

3-Acetyl-1,2,3,4,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole (2.07g, 8.12 mmol) was dissolved in EtOH and hydrogenated over 10% Pd on carbon (0.25g) in a Parr shaker at 55 lbs of hydrogen pressure. After 5 hrs, the reaction mixture was filtered through Celite to remove the catalyst and the filtrate was concentrated under reduced pressure to give a residue which was purified by chromatography on silica gel eluting with 0.3-2% MeOH in methylene chloride to give

1.84g (87%) of 3-acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]-diazepino[6,7,1-hi]indole as a white solid, mp:111-113°C.

Anal. Calcd for $C_{16}H_{20}N_2O$ + .20 H_2O

Theory: %C, 73.93; %H, 7.91; %N, 10.78.

Found: %C, 74.05; %H, 7.91; %N, 10.79.

3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole was dissolved in conc. HCl and heated with stirring in an oil bath (110°C) for 12 hr. After cooling, the reaction mixture was made basic with 2.5N NaOH and 50% NaOH, extracted into methylene chloride, dried ($MgSO_4$), filtered and concentrated to give a residue. The residue was purified by chromatography on silica gel eluting with 1-20% MeOH in methylene chloride to give the product of Example 24 as a yellow solid, mp: 76-79 °C.

Example 26

The compound of Example 24 was chromatographed on a Chiralal column eluting with MeOH containing 0.1% diethylamine.

Peak one was obtained as a yellow solid, mp: 51-54°C and identified (7bS,10aS)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]-indole.

Anal. Calcd for $C_{14}H_{18}N_2$ +0.20 H_2O

Theory: %C, 78.46;%H, 8.47;%N, 13.07.

Found: %C, 77.09;%H, 8.50;%N, 12.72.

Peak two was obtained as a yellow solid, mp: 43-46°C. This peak was identified as a mixture of 92.3% (7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]indole and 7.7% of identified (7bS,10aS)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole.

Example 27

3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole (Example No. 25) was chromatographed on a Chiralcel AD chiral column (20 x 250 mm) eluting with 100% MeOH at room temperature, detection method: UV/VIS at 254 nm..

A. Peak one was obtained as a colorless viscous oil, identified as (7bS,10aS)-3-acetyl-1,2,3,4,8,9,10,10a-Octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole.
Anal. Calcd. for $C_{16}H_{20}N_2O$ + .60 H_2O
Theory: %C, 71.93; %H, 8.00; %N, 10.49.
Found: %C, 72.06; %H, 7.79; %N, 10.73.

O.R.:[alpha]25/D=+118(19.2mg/mL) MeOH)

(7bS,10aS)-3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]-diazepino[6,7,1-hi]indole was treated with solid NaOH in MeOH under reflux to give (7bS,10aS)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino-[6,7,1-hi]-indole mp: 54-56 °C.
O.R.: [alpha]25/D=+134.18 (10.359mg/mL, MeOH)

B. Peak two was obtained as a colorless viscous oil, identified as (7bR,10aR)-3-acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole.
Anal. Calcd. for $C_{16}H_{20}N_2O$ + .80 H_2O
Theory: %C, 70.98; %H, 8.04; %N, 10.35
Found: %C, 70.94; %H, 7.73; %N, 10.22
O.R.: [alpha]25/D=-132 (10.2mg/mL MeOH)

(7bR,10aR)-3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]-diazepino-[6,7,1-hi]indole was treated with solid NaOH in MeOH under reflux to give (7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]-indole mp: 57-59°C

Anal Calcd for $C_{14}H_{18}N_2$

Theory: %C,77.81; %H,8.49; %N, 12.96.

Found: %C,78.01; %H,8.64; %N, 12.90.

Example 28 (chiral salt resolution of Example No. 24)

(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]indole

The compound of Example 24 (10.0 g, 46.7 mmol) was dissolved in isopropanol (500 mL) at 65-70 °C under nitrogen and dibenzoyl-L-tartaric acid (4.18 g, 11.7 mmol) was added all at one time. The resultant solids were slurried at 70-75°C for two h, cooled to room temperature and stored at 10°C for 12 h. The solids were filtered and washed twice with isopropanol (15 mL). The solids were reslurried in hot (80°C) isopropanol (400 mL) for 1.5 h, cooled to room temperature and stored at 10 °C for 12 h. The solids were filtered and washed twice with isopropanol (15 mL) and air dried to give 7.3g (79.9%) of the dibenzoyl-L-tartaric acid salt of the title compound as a white solid, mp: 163-5 °C.

Anal. Calcd for $C_{14}H_{18}N_2 \cdot 0.5\ C_{18}H_{14}O_8 \cdot 0.4\ C_3H_8O$

Calcd: %C, 69.60; %H, 6.75; %N, 6.70.

Found: %C, 69.80; %H, 6.73; %N, 6.58.

O.R.: [alpha]25/D=-138.4 (1 mg/mL, MeOH)

The above tartrate salt (9.5 g, 12.1 mmol) was slurried in ethyl acetate (950 mL) and 1 N hydrochloric acid was added (25.0 mL, 25.0 mmol). The slurry was

concentrated by atmospheric distillation (72-77 °C) to a volume of 275 mL, cooled to room temperature and stored overnight at 10°C. The solids were filtered and washed twice with ethyl acetate (20 mL) and air dried to give 5.7 g (92.8 %) of the hydrochloride salt of the title compound as a white solid, mp 246-249°C decomposed.

The HCl salt (5.6 g) was dissolved in ethanol (100 mL) at reflux. Upon cooling to room temperature, needle-like crystals formed. The mixture was stored overnight at 10°C. The solids were filtered, washed twice with ethanol (10 mL) and vacuum dried (57°C /0.1mm) to give 3.8 g (67.8 %) of white solid, mp 252-253°C decomposed.

Anal. Calcd for $C_{14}H_{18}N_2 \cdot HCl$

Calcd: %C, 67.05; %H, 7.64; %N, 11.17.

Found: %C, 66.74; %H, 7.54; %N, 11.09.

Example 29

1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]Diazepino[6,7,1-*hi*]Indole

A. 1,2,3,4-Tetrahydrocyclopenta[*b*]Indole

Concentrated sulfuric acid (~18 M, 35 mL) was added dropwise to a mixture of phenyl hydrazine (510 mmol, 50 mL) and cyclopentanone (45 mL, 510 mmol) in water (250 mL). The resulting mixture was heated to reflux for 30 min and then allowed to cool to room temperature. The liquid was decanted from the reaction mixture leaving a red, gummy solid. Hexanes (500-600 mL) was added to the flask and the mixture was heated to reflux. The yellow hexane solution was decanted hot from the mixture and placed in the freezer (crystallization begins immediately). More hexanes is added to the flask and the procedure repeated two more times using a total volume of 1500 mL of hexanes. After 1 h in the freezer, the solid was collected from the flasks and dried providing the known indole (410 mmol, 65 g, 80%).

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91

Found: C, 83.92; H, 7.12; N, 8.85

B. 1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indole

A mixture of 1,2,3,4-tetrahydrocyclopenta[*b*]indole (11 mmol, 1.8 g), 5% Pd/C (0.5 g), and concentrated hydrochloric acid (1.2 mL) was hydrogenated at 45 psi on a Parr shaker. After 3 h, the mixture was removed from the shaker and filtered through Celite. The solid bed was washed with methanol. The filtrate was concentrated. The crude oil was dissolved in 1 N HCl and washed with ether. The aqueous phase was treated with 2.5 N NaOH to pH >10 and then extracted with chloroform. The combined chloroform extracts were dried over $MgSO_4$, filtered and concentrated to give the crude indoline. The material was purified by flash column chromatography through silica gel (Biotage, elution with 10% ethyl acetate-hexanes) to give the known indoline (7.6 mmol, 1.2 g, 69%) as a clear oil.

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80

Found: C, 82.61; H, 8.35; N, 8.72

C. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]Indol-4(1*H*)-yl)Acetamide

To a stirred solution of 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (130 mmol, 21 g) in DMF (50 mL) was added diisopropylethylamine (400 mmol, 70 mL) followed by 2-chloroacetamide (270 mmol, 25 g). The reaction mixture was heated to 100°C for 18 h. The reaction was concentrated and the diluted with ethyl acetate and water. The phases were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash column chromatography through silica gel (elution with 60% ethyl acetate-hexanes) to afford a yellow solid (90 mmol, 20 g, 69%).

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95.

Found: C, 72.45; H, 7.57; N, 12.64.

MS ((+)APCI, m/e(%)) 217(100, $[M+H]^+$).

IR (solid ATR, cm^{-1}) 3450, 2930, 2870, 1680, 1480, 1150, 740.

^1H NMR (DMSO-d_6, 400MHz) δ 7.20(s, 1H), 7.05(s, 1H), 6.90(m, 2H), 6.48(dt, J=0.73Hz, 7.3Hz, 1H), 6.18(d, J=7.8Hz, 1H), 4.22(m, 1H), 3.70, 3.58(ABq, J_{AB}=17.1Hz, 2H), 3.64(m, 1H), 1.90(m, 1H), 1.78(m, 1H), 1.56(m, 3H), 1.40(m, 1H).

D. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]Indol-4(1*H*)-yl)Acetonitrile

To a stirred solution of 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (22 mmol, 3.5 g) in DMSO (44 mL) was added 60% sodium hydride (24 mmol, 0.97 g) portionwise, followed by 2-chloroacetonitrile (33 mmol, 2.1 mL). The reaction mixture stirred at ambient temperature for 18 h and then additional 60% sodium hydride (22 mmol, 0.88 g) and 2-chloroacetonitrile (24 mmol, 1.5 mL) was added. The reaction was heated to 60°C for 18 h. The reaction was concentrated and the diluted with ethyl acetate and water. The phases were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash column chromatography through silica gel (elution with 60% ethyl acetate-hexanes) to afford the desired material.

^1H NMR (DMSO-d_6, 400MHz) δ 7.25(s, 1H), 7.05(m, 1H), 6.78(m, 1H), 6.46(m, 1H), 4.30-3.70(m, 4H), 2.10-1.50 (m, 6H).
MS ((-)APCI, m/e(%)) 198(40, [M]).

E. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]Indol-4(1*H*)-yl)Ethylamine

2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)acetamide (90 mmol, 20 g) was dissolved in 1 M BH_3•THF (200 mL) and heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature and then quenched slowly with methanol. The solution was concentrated, dissolved in methanol, and again concentrated. The resulting oil was diluted with ether and

extracted twice with 1 N HCl. The aqueous phase was treated with 2.5 N NaOH to pH >10 and extracted with chloroform. The combined chloroform extracts were dried over $MgSO_4$, filtered and concentrated to provide a yellow oil.

Anal. Calcd. for $C_{13}H_{18}N_2 \cdot 0.55mol\ H_2O$: C, 73.58; H, 9.07; N, 13.20.

Found: C, 73.62; H, 8.80; N, 12.83.

MS (EI, m/e(%)) 202(10, M^+), 172(100), 130(20).

IR (film ATR, cm^{-1}) 2950, 2870, 1605, 1480, 1250(br), 730.

^1H NMR (DMSO-d_6, 400MHz) δ 6.89(dd, J=0.73Hz, 7.3Hz, 2H), 6.42(dt, J=0.73Hz, 7.3Hz, 1H), 6.29(d, J=7.6Hz, 1H), 4.12(m, 1H), 3.62(dt, J=2.4Hz, 9.0Hz, 1H), 3.08(m, 2H), 2.65(m, 2H), 1.90(m, 1H), 1.75(m, 1H), 1.58(m, 3H), 1.43(m, 1H).

F. <u>1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]-Diazepino[6,7,1-*hi*]-Indole</u>

A solution of 2-(2,3,3a,8b-tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)ethylamine (25 mmol, 5.0 g) was dissolved in ethanol (125 mL) at room temperature and trifluoroacetic acid (25 mmol, 1.9 mL) was added, followed by aqueous formaldehyde(25 mmol, 37%, 1.9 mL). The reaction was heated to reflux for one hour and an aliquot was removed, concentrated and an NMR taken, which showed the reaction complete. The reaction vessel was cooled and then concentrated *in vacuo*. The resulting oil was partitioned between $CHCl_3$ and 1N NaOH. The aqueous phase was extracted again with $CHCl_3$. The combined organics were washed with 1N NaOH, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a brown oil (23.8 mmol). The crude product was purified by flash chromatography (SiO_2) eluting with 5%MeOH/$CHCl_3$ to yield a yellow waxy solid (13 mmol, 2.7 g, 52%).

Anal. Calcd. for $C_{14}H_{18}N_2 \cdot 0.15mol\ H_2O$:C, 77.49; H, 8.50; N, 12.91.

Found: C, 77.13; H, 8.07; N, 12.77.

MS ((+)APCI, m/e(%)) 215(100, $[M+H]^+$).

IR (solid ATR, cm^{-1}) 3210, 2910, 2860, 2810, 1590, 1460, 1430, 1340, 1290, 750.

^1H NMR (DMSO-d_6, 400MHz) δ 6.85(d, J=7.3Hz, 1H), 6.72(d, J=7.1Hz, 1H), 6.52(t, J=7.3Hz, 1H), 3.89(m, 1H), 3.8, 3.48(ABq, J_{AB}=15.13Hz, 2H), 3.69(dt, J=2.9Hz, 1H), 3.08(m, 2H), 2.71(m, 1H), 2.62(m, 1H), 2.29(br m, 1H), 1.90(m, 1H), 1.76(m, 1H), 1.68-1.48(m, 3H), 1.40(m, 1H).

Example 30

***rel*-(4*S*,7b*S*,10a*S*)-4-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]-Diazepino[6,7,1-*hi*]Indole**

2-(2,3,3a,8b-tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)ethylamine (4.9 mmol, 1.0 g) was dissolved in ethanol (25 mL) at room temperature and trifluoroacetic acid (4.9 mmol, 380 μL) was added, followed by acetaldehyde (4.9 mmol, 37%, 280 μL). The reaction was heated to reflux overnight. The reaction vessel was cooled and then concentrated *in vacuo*. The resulting oil was partitioned between $CHCl_3$ and 1N NaOH. The aqueous phase was extracted again with $CHCl_3$. The combined organics were washed with 1N NaOH, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a brown oil (23.8 mmol). The crude product was purified by flash chromatography (SiO_2) eluting with 10%MeOH/$CHCl_3$ to give the two racemic diastereomers.

Less Polar Product:

Rf 0.5 (A) 10%Et_3N/EtOAc

MS ((+)APCI, m/e(%)) 229(100, $[M+H]^+$).

IR (film ATR, cm^{-1}) 2940, 2860, 1600, 1460, 1430, 1330, 1300, 1230, 1070, 750.

^{1}H NMR (DMSO-d_6, 400MHz) δ 6.88(d, J=7.3Hz, 1H), 6.81(d, J=7.8Hz, 1H), 6.59(t, J=7.4Hz, 1H), 3.87(m, 1H), 3.71(m, 1H), 3.45(q, J=6.7Hz, 1H), 3.06(m, 2H), 2.80-2.67(m, 2H), 2.05(br m, 1H), 1.90(m, 1H), 1.75(m, 1H), 1.64(m, 1H), 1.52(m, 2H), 1.37 (m, 1H), 1.37(d, J=6.8Hz, 3H).

Example 31

***rel*-(4*R*,7b*S*,10a*S*)-4-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]-Diazepino[6,7,1-*hi*]Indole**

Prepared in Example 30 isolating the more polar product.

Rf 0.39 (B) 10%Et_3N/EtOAc

MS ((+)APCI, m/e(%)) 229(100, $[M+H]^+$).

IR (film ATR, cm^{-1}) 2950, 2930, 2860, 1600, 1460, 1430, 1320, 1230, 1050, 750.

^{1}H NMR (DMSO-d_6, 400MHz) δ6.81(d, J=7.1Hz, 1H), 6.71(d, J=7.6Hz, 1H), 6.52(t, J=7.3Hz, 1H), 4.0(q, J=6.9Hz, 1H), 3.82(dd, J=4.7Hz, 8.6Hz, 1H), 3.68(dt, J=2.7Hz, 8.9Hz, 1H), 3.05(m, 2H), 2.82-2.70(m, 2H), 2.3(br m, 1H), 1.88(m, 1H), 1.78(m, 1H), 1.64-1.48(m, 3H), 1.40(m, 1H), 1.17(d, J=7.1Hz, 3H).

Example 32

(2*S*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

A. 1,2,3,4-Tetrahydrocyclopenta[*b*]Indole-5-Carboxylic Acid

To a stirred solution of 2-hydrazinobenzoic acid hydrochloride (53 mmol, 10.0 g) and cyclopentanone (58 mmol, 4.9 g) in 1,4-dioxane (100 mL) was added dropwise concentrated H_2SO_4 (~18M, 63 mmol, 3.5 mL). The resulting solution was heated to reflux for 2 hours. ^{1}H NMR analysis of a crude aliquot indicated complete reaction. The reaction was allowed to cool to room temperature and then concentrated to dryness to give a red solid which was used without further purification.

^{1}H NMR (DMSO-d_6, 300MHz) δ 10.8(s, 1H), 7.6-7.0(m, 3H), 2.8(m, 4H), 2.4(m, 2H).

B. Ethyl (2*S*)-2-[(1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoate

To a stirred, cooled (0°C) solution of crude 1,2,3,4-tetrahydrocyclopenta[*b*]-indole-5-carboxylic acid (60 mmol, 12 g), L-alanine ethyl ester (72 mmol, 11 g), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (72 mmol, 14 g), 1-hydroxybenzotriazole (HOBT) (72 mmol, 10 g) in CH_2Cl_2 (100 mL) was slowly added diisopropylethylamine (360 mmol, 46 g). The reaction mixture was stirred overnight while warming to room temperature. The reaction was concentrated *in vacuo* and the resulting oil was partitioned between water and ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated to a brown oil. The crude material was purified by chromatography through silica gel (Biotage) eluting with 15% ethyl acetate-hexanes to afford a yellow oil (8.4 mmol, 2.5 g, 14%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 10.9(s, 1H), 8.74(d, 1H), 7.62(d, 1H), 7.48(d, 1H), 6.98(t, 1H), 4.47(t, 1H), 4.08(m, 2H), 2.75(m, 4H), 2.40(m, 2H), 1.42(d, 3H), 1.15(t, 3H).

C. Ethyl (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)-Amino]Propanoate

A solution of ethyl (2*S*)-2-[(1,2,3,4-tetrahydrocyclopenta[*b*]indol-5-ylcarbonyl)-amino]propanoate (8.4 mmol, 2.5 g) in ethanol (40 mL) was added to a mixture of 5% palladium on carbon (2 g) in ethanol (20mL). Concentrated hydrochloric acid (10 mL) was added and the resulting mixture was hydrogenated at 45 psi for 4 hours. The reaction mixture was filtered through Celite. The filter bed was washed well with ethanol and the combined filtrates were concentrated. The resulting oil was partitioned between 1 N NaOH and ethyl acetate. The orgainc phase was dried over $MgSO_4$, filtered and concentrated to yield an oil (1.9 g, 6.1 mmol, 73%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 8.7(m, 1H), 7.63(m, 1H), 7.25(m, 1H), 6.85(m, 2H), 4.40(m, 2H), 4.10(m, 2H), 3.76(m, 1H), 1.90(m, 2H), 1.68(m, 3H), 1.38(d, 3H), 1.31(m, 1H), 1.16(t, 3H).

D. (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoic Acid

A 1 M aqueous lithium hydroxide solution (13 mmol, 13 mL) was added to a solution of ethyl (2*S*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-ylcarbonyl)-amino]propanoate (6.1 mmol, 1.9 g) in THF (50 mL). The reaction mixture was stirred at room temperature for 18 h. The reaction was concentrated *in vacuo* and diluted with 0.1 N HCl and ethyl acetate. The phases were separated and the organic phase was

washed with water, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil (1.6 g, 6.1 mmol, quantitative).

^{1}H NMR (DMSO-d_6, 300MHz) δ 12.4(s, 1H), 8.21(d, 1H), 7.43(m, 1H), 7.01(d, 1H), 6.70(br s, 1H), 6.40(t, 1H), 4.35(m, 2H), 3.63(t, 1H), 1.88(m, 2H), 1.62(m, 4H), 1.30(d, 3H).

E. (2*S*)-2-Methyl-2,3,8,9,10,10a-Hexahydro-7b*H*-Cyclopenta[*b*][1,4]Diazepino-[6,7,1-*hi*]Indole-1,4-Dione

A solution of (2*S*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-yl-carbonyl)amino]propanoic acid (6.1 mmol, 1.6 g) was dissolved in acetic acid (50 mL) and heated to reflux for 18 h. The reaction was allowed to cool to room temperature and was concentrated to dryness. The crude material was purified by flash column chromatography (silica gel; 1:1 ethyl acetate-hexanes) to provide two diastereomers: less polar product (0.88 mmol, 0.23 g, 14%) and more polar product (0.18 mmol, 45 mg, 3%). The mixed fractions were also collected to provide another 3.9 mmol (1.0 g, 64%) of material.

Less Polar Product (A)
^{1}H NMR (DMSO-d_6, 300MHz) δ 8.2(d, 1H), 7.61(m, 1H), 7.46(dd, 1H), 7.16(t, 1H), 4.86(dt, 1H), 3.87(m, 2H), 1.92(m, 2H), 1.75(m, 1H), 1.58(m, 2H), 1.26(d, 3H), 1.06(m, 1H).

F. (2*S*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclo-penta[*b*][1,4]Diazepino[6,7,1-*hi*]Indole

A mixture of diastereomers of (2*S*)-2-methyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (3.9 mmol, 1.0 g) was suspended in 1 M BH_3•THF (15 mL) and heated to reflux for 18 h. After cooling to

room temperature, the solution was quenched with methanol and concentrated. The resulting solid was suspended in 1 N NaOH and stirred at room temperature for 1 h. The aqueous phase was then extracted with chloroform and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to give a yellow solid (3.5 mmol, 0.80 g, 90%). Flash chromatography through silica gel (gradient elution 5%-10% methanol-chloroform) afforded the two diastereomers. The less polar product was arbitrarily assigned the *R,R* configuration and the more polar product the *S,S* configuration.

Anal. Calcd. for $C_{15}H_{20}N_2 \cdot 1.5mol\ H_2O$: C, 70.56; H, 9.08; N, 10.97.

Found: C, 70.24; H, 9.58; N, 10.81.

MS ((+))APCI, m/e (%)) 229(100, $[M+H]^+$).

IR (solid ATR, cm^{-1}) 2960, 2880, 2310, 1460, 1440, 1210, 1160, 1120, 1090, 1070.

^1H NMR (DMSO-d_6, 400MHz) δ 7.32(t, J=7.56Hz, 1H), 7.22(d, J=7.3Hz, 1H), 7.12(d, J=7.3Hz, 1H), 4.35(m, 1H), 4.07(m, 2H), 3.82(d, J=16.84Hz, 1H), 3.62(m, 1H), 3.14(dd, J=8.54Hz, 10.74Hz, 1H), 3.0(m, 1H), 2.04-1.69(m, 4H), 1.51(m, 2H), 1.22(d, J=6.6Hz, 4H).

$[\alpha]_D$ +99 (c. 0.11, DMSO).

Example 33

(2*S*)-(*rel*-7b*S*,10a*S*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

Following the procedure of Example 32F, the more polar material provided the product which was assigned the *S,S* configuration.

Anal. Calcd. for $C_{15}H_{20}N_2 \cdot 1.1mol\ H_2O$: C, 72.60; H, 9.02; N, 11.29.

Found: C, 72.63; H, 8.80; N, 10.95.

MS ((+)APCI, m/e (%)) 229(100, $[M+H]^+$).

^{1}H NMR (DMSO-d_6, 400MHz) δ 6.86(d, J=7.3Hz, 1H), 6.73(d, J=7.3Hz, 1H), 6.52(t, J=7.4Hz, 1H), 3.95(m, 2H), 3.82(d, J=15.86Hz, 1H), 3.61(m, 1H), 3.41(dd, J=3.17Hz, 13.4Hz, 2H), 3.21(m, 1H), 2.83(dd, J=3.9Hz, 13.2Hz, 1H), 1.94(m, 1H), 1.77(m, 1H), 1.55(m, 4H), 1.15(d, J=6.6Hz, 3H).

$[\alpha]_D$ +38 (c. 0.10, DMSO).

Example 34

(2*R*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

A. **Methyl (2*R*)-2-[(1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoate**

Following the procedure of method 1B, employing D-alanine methyl ester (64 mmol, 8.9 g) afforded a yellow oil (4.9 mmol, 1.4 g, 8%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 10.8(s, 1H), 8.78(d, 1H), 7.61(d, 1H), 7.49(d, 1H), 7.0(t, 1H), 4.5(m, 1H), 3.63(s, 3H), 2.76(m, 4H), 2.42(m, 2H), 1.42(d, 3H).

B. **Methyl (2*R*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)-Amino]Propanoate**

Following the procedure of method 1C, methyl (2*R*)-2-[(1,2,3,4-tetrahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]propanoate (4.9 mmol, 1.4 g) was hydrogenated using 5% Pd/C (1.5 g) and concentrated HCl (7 mL) in methanol (25 mL) to yield an oil (2.7 mmol, 0.77 g, 55%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 8.34(d, 1H), 7.44(d, 1H), 7.02(d, 1H), 6.70(s, 1H), 6.41(t, 1H), 4.39(m, 2H), 3.65(m, 1H), 3.60(s,3H), 1.89(m, 1H), 1.61(m, 4H), 1.35(d, 3H), 1.29(m, 1H).

C. **(2*R*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)Amino]-Propanoic Acid**

Following the procedure of method 1D, methyl (2*R*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]propanoate (2.7 mmol, 0.77 g) was hydrolyzed to the acid using 1 M aqueous lithium hydroxide (5.9 mL) in THF (20 mL) to yield an orange oil which was used without further purification.

^{1}H NMR (DMSO-d_6, 300MHz) δ 12.4(br s, 1H), 8.2(d, 1H), 7.43(d, 1H), 7.01(d, 1H), 6.9(br s, 1H), 6.4(t, 1H), 4.33(m, 2H), 3.62(t, 1H), 1.89(m, 2H), 1.61(m, 4H), 1.32(d, 3H).

D. **(2*R*)-2-Methyl-2,3,8,9,10,10a-Hexahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino-[6,7,1-*hi*]Indole-1,4-Dione**

Following the procedure of method 1E, (2*R*)-2-[(1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indol-5-ylcarbonyl)amino]propanoic acid was cyclized by refluxing in acetic acid (50 mL). Purification by flash chromatography through silica gel (elution with 5% methanol-chloroform) provided each diastereomer: less polar product (1.5 mmol, 0.39 g, 56% over 2 steps) arbitrarily assigned as the *R,R* configuration and more polar product (0.47 mmol, 0.11 g, 17% over 2 steps) assigned as the *S,S* configuration.

Less Polar Product (A)

^{1}H NMR (DMSO-d_6, 300MHz) δ 8.2(d, 1H), 7.62(d, 1H), 7.46(d, 1H), 7.16(t, 1H), 4.87(m, 1H), 3.88(m, 2H), 1.94(m, 3H), 1.76(m, 1H), 1.59(m, 2H), 1.28(d, 3H).

E. **(2*R*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta-[*b*][1,4]Diazepino[6,7,1-*hi*]Indole**

Following the procedure of method 1F, (2*R*)-(*rel*-7b*R*,10a*R*)-2-methyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*]-[1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (1.5 mmol, 0.39 g) was reduced with 1 M BH_3•THF (10 mL) to yield a yellow solid (0.47 mmol, 0.11 g, 31%).

Anal. Calcd. for $C_{15}H_{20}N_2 \cdot 0.15mol\ H_2O$: C, 77.98; H, 8.86; N, 12.12.

Found: C, 77.72; H, 9.03; N, 11.89.

MS ((+)ESI, m/e(%)) 457(17, $[2M+H]^+$), 307(81, $[M+H+DMSO]^+$), 229(100, $[M+H]^+$).

IR (solid ATR, cm^{-1}) 3240, 2950, 2870, 1590, 1460, 1350, 1290, 1270, 740.

^1H NMR (DMSO-d_6, 400MHz) δ 6.8(d, J=7.1Hz, 1H), 6.65(d, J=7.1Hz, 1H), 6.47(t, J=7.3Hz, 1H), 3.94(m, 1H), 3.80, 3.71(ABq, J_{AB}=16.1Hz, 2H), 3.59(m, 1H), 3.35(dd, J=3.17Hz, 12.93Hz, 1H), 3.02(m, 1H), 2.75(dd, J=4.39Hz, 12.93Hz, 1H), 2.49(m, 1H), 1.94(m, 1H), 1.76(m, 1H), 1.56(m, 4H), 1.07(d, J=6.6Hz, 3H).

$[\alpha]_D$ -82 (c. 0.10, DMSO).

Example 35

(2*R*)-(*rel*-7b*S*,10a*S*)-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*]-[1,4]Diazepino[6,7,1-*hi*]Indole

Following the procedure of Example 32F, (2*R*)-(*rel*-7b*S*,10a*S*)-2-methyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*]-[1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (0.47 mmol, 0.11 g) was reduced with 1 M BH_3•THF (8 mL) to yield the product (0.27 mmol, 61 mg, 57%).

MS ((+)APCI, m/e (%)) 457(20, $[2M+H]^+$), 229(100, $[M+H]^+$).

^{1}H NMR (DMSO-d_6, 400MHz) δ 6.85(d, J=7.08Hz, 1H), 6.72(d, J=7.3Hz, 1H), 6.52(t, J=7.3Hz, 1H), 3.82(dd, J=5.6Hz, 9.0Hz, 1H), 3.79, 3.51(ABq, J_{AB}=15.1Hz, 2H), 3.70(dt, J=2.9Hz, 9.0Hz, 1H), 3.28(m, 1H), 3.06(dd, J=2.1Hz, 12.1Hz, 1H), 2.78(m, 1H), 2.43(m, 1H), 1.92-1.30(m, 6H), 1.02(d, J=6.6Hz, 3H).

Example 36

(2*R*,7b*S*,10a*S*)-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]Diazepino-[6,7,1-*hi*]Indol-2-ylmethanol

A. **Methyl (2*S*)-3-Hydroxy-2-[(1,2,3,4-Tetrahydrocyclopenta[*b*]Indol-5-yl-carbonyl)Amino]Propanoate**

Following the procedure of Example 32B, employing L-serine methyl ester (64 mmol, 9.9 g) afforded a yellow solid (8.9 mmol, 2.7 g, 14%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 10.8(s, 1H), 8.51(d, 1H), 7.61(d, 1H), 7.51(d, 1H), 7.01(t, 1H), 5.08(m, 1H), 4.56(q, 1H), 3.82(d, 2H), 3.62(s, 3H), 2.76(m, 4H), 2.42(m, 2H).

B. Methyl (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl)-Amino]-3-Hydroxypropanoate

Following the procedure of Example 32C, methyl (2*S*)-3-hydroxy-2-[(1,2,3,4-tetrahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]propanoate(8.9 mmol, 2.7 g) was hydrogenated using 5% Pd/C (2 g) and concentrated HCl (10 mL) in methanol (25 mL) to yield the crude product (8.9 mmol, 2.7 g, quantitative).

^{1}H NMR (DMSO-d_6, 300MHz) δ 8.3(d, 1H), 7.86(d, 1H), 7.34(d, 1H), 7.03(t, 1H), 5.80(br s, 2H), 4.45(m, 2H), 3.80(m, 2H), 3.61(s, 3H), 2.0-1.55(m, 6H).

B. (2*S*)-2-[(1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]Indol-5-ylcarbonyl]Amino}-3-Hydroxypropanoic Acid

Following the procedure of Example 32D, methyl (2*S*)-2-[(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-5-ylcarbonyl)amino]-3-hydroxypropanoate (8.9 mmol, 2.7 g) was hydrolyzed to the acid using 1 M aqueous lithium hydroxide (40 mL) in THF (40 mL) to yield a red oil (1.5 mmol, 430 mg, 17%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.92(d, 1H), 7.40(d, 1H), 7.03(d, 1H), 6.43(t, 1H), 4.39(m, 2H), 3.63(br m, 4H), 2.0-1.2(m, 6H).

C. (2*S*)-2-(Hydroxymethyl)-2,3,8,9,10,10a-Hexahydro-7b*H*-Cyclopenta[*b*]-[1,4]-Diazepino[6,7,1-*hi*]Indole-1,4-Dione

Following the procedure of Example 32E, (2*S*)-2-[(1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indol-5-ylcarbonyl)amino]-3-hydroxypropanoic acid (1.5 mmol, 430 mg) was cyclized by refluxing in acetic acid (40 mL). Purification by flash chromatography through silica gel (elution with 5% methanol-chloroform) provided each diastereomer: less polar product (0.55 mmol, 0.15 g, 37%) arbitrarily assigned as the *R,R* configuration and more polar product (0.26 mmol, 0.070 g, 17%) assigned as the *S,S* configuration.

Less Polar Product (A)

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.44(d, 1H), 7.63(d, 1H), 7.48(d, 1H), 7.19(m, 1H), 4.88(m, 1H), 4.39(dd, 1H), 4.22(t, 1H), 4.07(m, 1H), 3.91(m, 1H), 2.0-1.5(m, 6H).

D. (2*R*)-(*rel*-7b*S*,10a*S*)-1,2,3,4,8,9,10,10a-Octahydro-7b*H*-Cyclopenta[*b*][1,4]-Diazepino[6,7,1-*hi*]Indol-2-ylmethanol

Following the procedure of Example 32F, (2*S*)-(*rel*-7b*S*,10a*S*)-2-hydroxymethyl-2,3,8,9,10,10a-hexahydro-7b*H*-cyclopenta[*b*]-[1,4]diazepino[6,7,1-*hi*]indole-1,4-dione (0.26 mmol, 0.070 g) was reduced with 1 M BH_3•THF (1 mL) to yield a solid (0.17 mmol, 0.046 g, 65%).

MS ((+)APCI, m/e(%)) 323(35, $[M+H+DMSO]^+$, 245(100, $[M+H]^+$).

^1H NMR (DMSO-d_6, 400MHz) δ 6.85(d, J=7.1Hz, 1H), 6.73(d, J=7.3Hz, 1H), 6.52(t, J=7.3Hz, 1H), 4.70(m, 1H), 3.86, 3.50(ABq, J_{AB}=14.9Hz, 2H), 3.85(m, 1H), 3.70(dt, J=2.9Hz, 9.0Hz, 1H), 3.35(m, 1H), 3.22(m, 2H), 2.64(m, 1H), 2.40(m, 1H), 1.90(m, 1H), 1.75(m, 1H), 1.60(m, 2H), 1.50(m, 1H), 1.40(m, 2H).

The ability of the compounds of this invention to act as $5HT_{2C}$ agonists was established is several standard pharmacological test procedures; the procedures used and results obtained are provided below.

Test Procedures

$5HT2_C$ Receptor Binding Test Procedure

To evaluate high affinity for the $5HT2_C$ receptor, a CHO (Chinese Hamster Ovary) cell line transfected with the cDNA expressing the human 5-hydroxytryptamine2_C ($h5HT2_C$) receptor was maintained in DMEM (Dulbecco's Modified Eagle Media) supplied with fetal calf serum, glutamine, and the markers: guaninephosphoribosyl transferase (GTP) and hypoxanthinethymidine (HT). The cells were allowed to grow to confluence in large culture dishes with intermediate changes of media and splitting. Upon reaching confluence, the cells were harvested by scraping. The harvested cells were suspended in half volume of fresh physiological phosphate buffered saline (PBS) solution and centrifuged at low speed (900 x g). This operation was repeated once more. The collected cells were then homogenized with a

polytron at setting #7 for 15 sec in ten volumes of 50 mM Tris.HCl, pH 7.4 and 0.5 mM EDTA. The homogenate was centrifuged at 900 x g for 15 min to remove nuclear particles and other cell debris. The pellet was discarded and the supernatant fluid recentrifuged at 40,000 x g for 30 min. The resulting pellet was resuspended in a small volume of Tris.HCl buffer and the tissue protein content was determined in aliquots of 10-25 microliter (µl) volumes. Bovine Serum Albumin (BSA) was used as the standard in the protein determination by the method of Lowry et al., (J. Biol. Chem., 193:265 (1951). The volume of the suspended cell membranes was adjusted with 50 mM Tris.HCl buffer containing: 0.1% ascorbic acid, 10 mM pargyline and 4 mM $CaCl_2$ to give a tissue protein concentration of 1-2 mg per ml of suspension. The preparation membrane suspension (many times concentrated) was aliquoted in 1 ml volumes and stored at -70 C until used in subsequent binding experiments.

Binding measurements were performed in a 96 well microtiter plate format, in a total volume of 200 µl. To each well was added: 60 µl of incubation buffer made in 50 mM Tris.HCl buffer, pH 7.4 and containing 4 mM $CaCl_2$; 20 µl of [^{125}I] DOI (S.A., 2200 Ci/mmol, NEN Life Science).

The dissociation constant, KD of [^{125}I] DOI at the human serotonin $5HT_{2C}$ receptor was 0.4 nM by saturation binding with increasing concentrations of [^{125}I] DOI. The reaction was initiated by the final addition of 100.0 µl of tissue suspension containing 50 µg of receptor protein. Nonspecific binding is measured in the presence of 1 µM unlabeled DOI added in 20.0 µl volume. Test compounds were added in 20.0 ml. The mixture was incubated at room temperature for 60 min. The incubation was stopped by rapid filtration. The bound ligand-receptor complex was filtered off on a 96 well unifilter with a Packard ® Filtermate 196 Harvester. The bound complex caught on the filter disk was dried in a vacuum oven heated to 60° C and the radioactivity measured by liquid scintillation with 40 µl Microscint-20 scintillant in a Packard TopCount® equipped with six (6) photomultiplier detectors.

Specific binding is defined as the total radioactivity bound less the amount bound in the presence of 1 μM unlabeled DOI. Binding in the presence of varying concentrations of test drugs is expressed as percent of specific binding in the absence of drug. These results are then plotted as log % bound vs log concentration of test drug. Non linear regression analysis of data points yields both the IC50 and the Ki values of test compounds with 95% confidence limits. Alternatively, a linear regression line of decline of data points is plotted, from which the IC50 value can be read off the curve and the Ki value determined by solving the following equation:

$$Ki = \frac{IC50}{1+L/KD}$$

where L is the concentration of the radioactive ligand used and the KD is the dissociation constant of the ligand for the receptor, both expressed in nM.

The following Ki's are provided for various reference compounds:

Ki value and 95% confidence interval.

Ritanserin	2.0 (1.3 - 3.1) nM
Ketanserin	94.8 (70.7 - 127.0) nM
Mianserin	2.7 (1.9 - 3.8) nM
Clozapine	23.2 (16.0 - 34.0) nM
Methiothepin	4.6 (4.0 - 6.0) nM
Methysergide	6.3 (4.6 - 8.6) nM
Loxapine	33.0 (24.0 - 47.0) nM
mCPP	6.5 (4.8 - 9.0) nM
DOI	6.2 (4.9 - 8.0) nM

Stimulation of [^{3}H] Inositol Monophosphate production by $5HT_{2C}$ agonists.

CHO cells transfected with the cDNA expressing the human 5-HT_{2C} receptor were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with

10% fetal bovine serum and non-essential amino acids. Upon reaching confluence the cells were harvested using PBS/EDTA and plated in 24 well plates at an initial density of 2.5 x 10^5 cells per well. One (1) ml of maintenance medium containing 1μCi/ml myo-[^{3}H] inositol was added to each well. After 48 hours labeling, the cells were washed once with 0.5 ml DMEM containing 25 mM HEPES and 10 mM LiCl, then preincubated with the medium for 30 min (antagonists were included in this period if tested). At the end of the preincubation, the medium was removed, the cells were then incubated with test compounds (in presence of antagonists if needed) for 30 min. The reaction was terminated by removal of the incubation solution and addition of 0.5 ml ice-cold 5% PCA, followed by 15 to 30 min incubation on ice. 200 μl of 0.5 M Tes/1.5 M K_2CO_3 was added to each well to neutralize to pH 7, and plates were left on ice for another 15 to 30 min to precipitate all salts. The liquid and solid phases were separated by centrifugation.

A portion (350μl) of the upper aqueous phase was applied to Dowex AG-1X8 (formate form, 100-200 mesh) columns. The columns were then washed stepwise with 10 ml of water and 10 ml of 25 mM ammonium formate to remove free myo-[^{3}H]inositol and deacylated phosphoinositol, respectively. Finally 10 ml of 0.2 M ammonium formate solution was applied to the columns to elute [^{3}H] inositol monophosphate ([^{3}H] IP_1) directly into scintillation vials. Of this eluate, 1 ml was used to determine radioactivity by scintillation counting.

Agonist-stimulated levels of [^{3}H]inositol monophosphate (IP_1) is expressed as a percentage of the response observed with a maximally effective concentration of 5-HT (10μM). A 3-parameter logistic function is used to generate estimate of EC_{50}/IC_{50}. Antagonists are tested in the presence of 10 μM 5-HT.

The following data are provided for various reference compounds:

5-HT	15.1 nM	EC_{50}
mCPP	46.8 nM	EC_{50}
	60%	E_{MAX} (relative to 5-HT)
SB200646	286 nM	IC_{50} (10μM 5-HT as agonist)

Effects of compounds on feeding behavior in rats

Eight (8) male Sprague-Dawley rats weighing 150-180g were separated into individual cages and acclimated to a powdered diet for 2 weeks. During this period and throughout the test procedure, the food cup and the animals were weighed daily. Following the acclimation period, animals were fasted for 24 hours and then injected with either vehicle or one of 4 doses of the test compound. Food intake was assessed at 2 and 24 hours following compound administration. Compounds to be evaluated were injected 1 -2 x per week until all animals had received all doses of the test compound. The order of doses were chosen using to a modified Latin Square design. Additional studies may be conducted in satieted rats at the start of the dark cycle. Compounds were injected i.p, s.c. or p.o. At the end of the study effects of the test compound on food intake was evaluated using a repeated measures ANOVA. Data were collected were 2 hour food intake (g). Data were subjected to one-way ANOVA with posthoc t-tests to assess group differences. Where appropriate, ED50 values were calculated. The ED50 value is the dose that produces a 50% reduction in food intake during the test period.

Results

Results from in vitro Test Procedures

Compound	$5HT_{2C}$ Affinity DOI/Agonist binding (Ki, nM)	$5HT_{2C}$ % Emax (5HT, 100%)	Stimulation of IP3 (EC50, nM)
Example 1	97		
Example 2	18	110	136
Example 4A	2021	40	1254
Example 4B	10	100	76
Example 6	985		

Results from in vivo $5HT_{2C}$ Food Intake in Rats (24 hr fast)

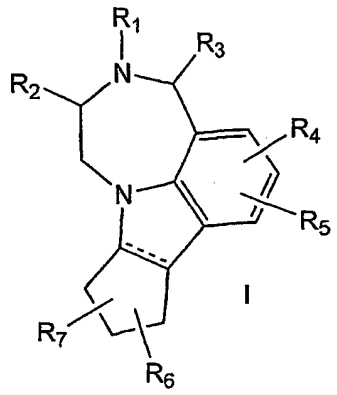
Compound	Route of Admin.	ED50 (mg/kg)
Example 2	ip	8.05
Example 4B	ip	2.93

Compound	5-HT_{2c} Affinity DOI/Agonist Binding (Ki, μM)
Example 7	6.0
Example 8	5.9
Example 9	0.91
Example 10	4.3
Example 11	1.9
Example 12	>5
Example 13	0.31

5

CLAIMS:

1. A compound of the formula:



I

wherein:

R_1 is hydrogen, alkyl of 1-6 carbon atoms, atoms, acyl of 2-7 carbon atoms, aryl, heteroaryl, or –C(O)R' wherein R' is alkyl of from 1 to 6 carbon atoms, aryl, or heteroaryl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl, of 3-7 carbon atoms, alkoxy of 1-6 carbon atoms, $-CH_2OH$, fluorinated alkyl of 1-6 carbon atoms, $-NH-SO_2$-alkyl of 1-6 carbon atoms, $-SO_2-NH$-alkyl of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aryl, heteroaryl, aroyl or heteroaroyl.

R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of 1-6 carbon atoms, -CN, $-NH-SO_2$-alkyl of 1-6 carbon atoms, $-SO_2-NH$-alkyl of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aroyl or heteroaroyl;

R_6 and R_7 are each independently hydrogen, C_1-C_6 alkyl, cycloalkyl of 3 to 7 carbon atoms or $-CH_2$-(cycloalkyl of 3 to 7 carbon atoms);

the dashed line indicates an optional double bond;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim wherein R_1 hydrogen, C_1-C_6 alkyl, benzoyl or alkanoyl of 2-7 carbon atoms.

3. A compound according to Claim 1 or Claim 2 wherein R_2 is or hydrogen, alkyl or fluorinated alkyl of 1-6 carbon atoms, -CH_2OH or cycloalkyl of 5-7 carbon atoms.

4. A compound according to any one of Claims 1 to 3 wherein R_3 is hydrogen, alkyl or fluorinated alkyl of 1-6 carbon atoms, -CH_2OH or cycloalkyl of 5-7 carbon atoms.

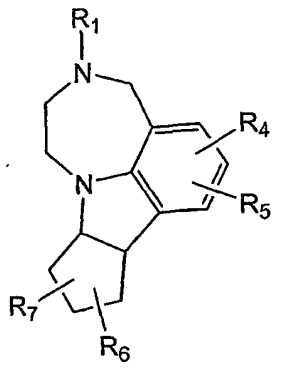
5. A compound according to any one of Claims 1 to 4 wherein R_4 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, -CN, amino or fluorinated alkyl of 1 to 6 carbon atoms.

6. A compound according to any one of Claims 1 to 5 wherein R_5 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, -CN, amino or fluorinated alkyl of 1 to 6 carbon atoms.

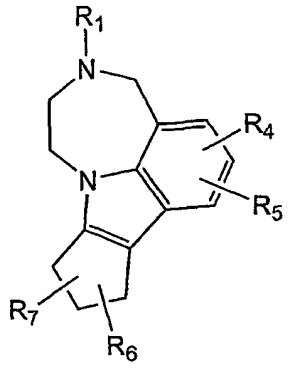
7. A compound according to any one of Claims 1 to 6 wherein R_6 is hydrogen or alkyl of 1-6 carbon atoms.

8. A compound according to any one of Claims 1 to 7 wherein R_7 is hydrogen or alkyl of 1-6 carbon atoms.

9. A compound of Claim 1 having one of the formulae:



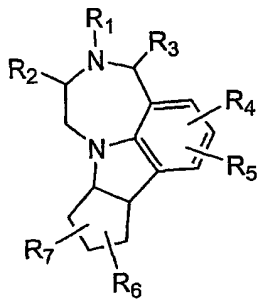
or



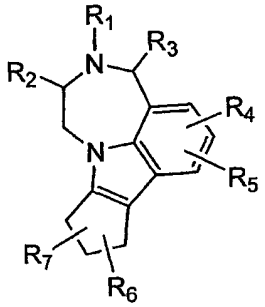
wherein R_1, R_4, R_5, R_6 and R_7 are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

10. A compound of Claim 1or Claim 9 wherein R_1 and R_7 are hydrogen and R_1, R_4, R_5, and R_6 are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

11. A compound of Claim 1 having one of the formulae:



or



wherein:

R_1 is hydrogen, or alkyl of 1-6 carbon atoms;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl, alkoxy of 1-6 carbon atoms, $-CH_2OH$, or fluorinated alkyl of 1 to 6 carbon atoms;

R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, -CN, amino or fluorinated alkyl of 1 to 6 carbon atoms;

R_6 and R_7 are each independently hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

12. A compound of Claim 1 which is one of the following:

1,2,3,4,9,10-Hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole;

1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole;

3-Acetyl-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta[b][1,4]diazepino[6,7,1-hi]-indole;

(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]-indole;

6-Methyl-1,2,3,4,9,10-hexahydro-8H-cyclopenta[b][1,4]diazepino[6,7,1-hi]indole;

(2*S*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]-diazepino[6,7,1-*hi*]Indole;

(2*S*)-(*rel*-7b*S*,10a*S*)-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]-diazepino[6,7,1-*hi*]indole;

(2*R*)-(*rel*-7b*R*,10a*R*)-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]-diazepino[6,7,1-*hi*]indole;

(2*R*)-(*rel*-7b*S*,10a*S*)-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]-diazepino[6,7,1-*hi*]Indole;

(2*R*,7b*S*,10a*S*)-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indol-2-ylmethanol;

rel-(4*S*,7b*S*,10a*S*)-4-Methyl-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]-diazepino[6,7,1-*hi*]indole, or

rel-(4*R*,7b*S*,10a*S*)-4-Methyl-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]-diazepino[6,7,1-*hi*]Indole

or a pharmaceutically acceptable salt thereof.

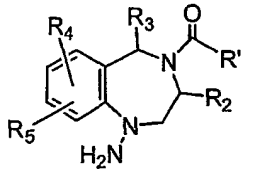
13. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to any one of Claims 1 to 12 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

14. A method of treatment of schizophrenia in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound according to any one of Claims 1 to 12 or a pharmaceutically acceptable salt thereof.

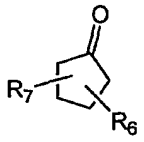
15. A method of treatment in a mammal of obsessive-compulsive disorder, depression, anxiety, panic disorder, anxiety, generalized anxiety disorder, obesity or epilepsy, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound according to any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof.

16. A process for preparing a compound of formula (I) as claimed in claim 1 which comprises one of the following:

a) reacting a compound of formula



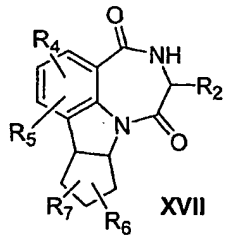
wherein R', R_2, R_3, R_4 and R_5 are as defined in Claim 1, with a compound of formula:



wherein R_6 and R_7 are as defined in Claim 1, and cyclising the resultant hydrazone, to give a corresponding compound of formula (I) wherein R_1 is -C(O)R' and the optional bond is present;

or

b) reducing a compound of formula

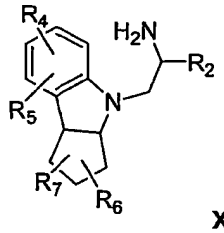


XVII

wherein R_2, R_4, R_5,R_6 and R_7 are as defined in Claim 1, with a reducing agent to give a corresponding compound of formula (I) wherein R_3 is hydrogen and the optional bond is absent;

or

c) reacting a compound of formula (XXIV):



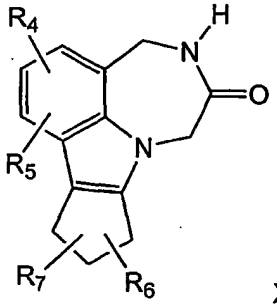
XXIV

wherein R_2, R_4, R_5,R_6 and R_7 are as defined in Claim 1, with a compound of formula

R_3CHO

wherein R_3 is as defined above, to give a corresponding compound of formula (I) wherein the optional bond is absent;

d) reducing a diazabenzo[*cd*]cyclopenta[*a*]azulen-6-one compound of formula XXXV:



XXXV

wherein R_4, R_5, R_6 and R_7 are as defined in Claim 1, with a reducing agent to a corresponding compound of formula (I) wherein R_2 is hydrogen;
or

e) reducing a compound of formula (I) as defined in Claim 1 wherein the optional bond is present to provide a compound of formula (I) wherein the optional bond is absent;

f) hydrolysing a compound of formula (I) as defined in Claim 1 wherein R_1 is acyl or -C(O)R' to give a compound of formula (I) wherein R_1 is hydrogen;
or

g) acylating a compound of formula (I) as defined in Claim 1 wherein R_1 is hydrogen with an acylating agent containing the group -C(O)R' to give a compound of formula (I) wherein R_1 is acyl or -C(O)R';
or

h) alkylating a compound of formula (I) as defined in Claim 1 wherein R_1 is hydrogen with an alkylating agent containing the group $-R_1$ wherein R_1 is alkyl or aryl to give a compound of formula (I) wherein R_1 is alkyl or aryl;
or

i) removing a protecting group from a compound of formula (I) as defined in Claim 1 in which at least one substituent carries a protecting group to give a compound of formula (I);
or

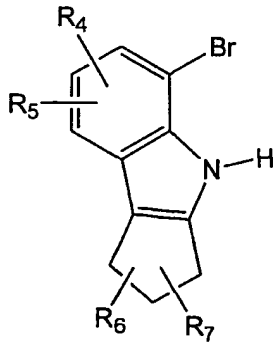
j) converting a basic compound of formula (I) as defined in Claim 1 to a salt thereof by reaction with a pharmaceutically acceptable acid or vice versa;
or

k) converting a compound of formula (I) as defined in Claim 1 having one or more reactive substituent groups to a different compound of formula (I);

or

l) isolating an isomer of a compound of formula (I) as defined in Claim 1 from a mixture thereof.

17. A compound of the formula:



wherein R_4, R_5, R_6 and R_7 are as defined in Claim 1, or Claims 5 to 8.

18. A compound of Claim 17 which is one of the following:

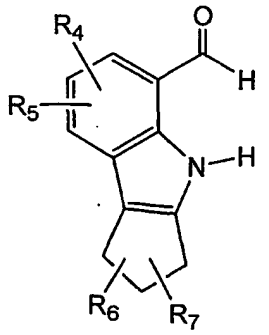
5-Bromo-1,2,3,4-tetrahydro-cyclopenta[*b*]indole;

5-Bromo-3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole;

5-Bromo-2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole, or

5-Bromo-1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole.

19. A compound of the formula:



wherein R_4, R_5, R_6 and R_7 are as defined in Claim 1 or Claims 5 to 8.

20. A compound of Claim 19 which is one of the following:

1,2,3,4-Tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde;

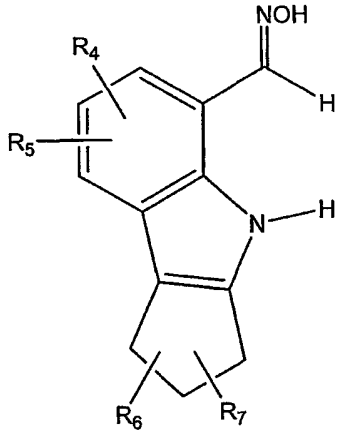
3-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde;

2-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde,

or

1-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde.

21. A compound of the formula:



wherein R_4, R_5, R_6 and R_7 are as defined in Claim 1or Claims 5 to 8.

22. A compound of Claim 21 which is one of the following:

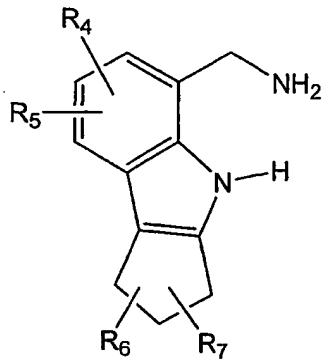
1,2,3,4-Tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime;

3-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime;

2-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime, or

1-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indole-5-carbaldehyde oxime.

23. A compound of the formula:



wherein $R4_1$, R_5, R_6 and R_7 are as defined in Claim 1 or Claims 5 to 8.

24. A compound of Claim 23 which is one of the following:

C-(1,2,3,4-Tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine;

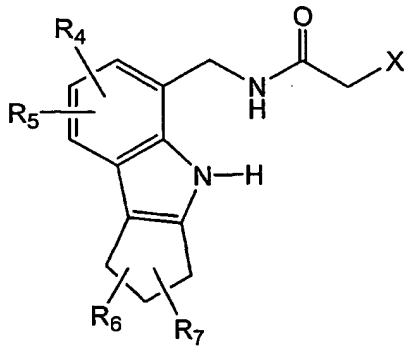
C-(3-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine;

C-(2-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine,

or

C-(1-Methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-yl)-methylamine.

25. A compound of the formula:



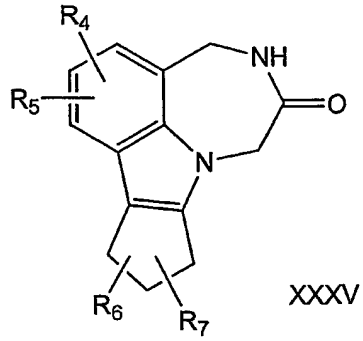
wherein R_4, R_5, R_6 and R_7 are as defined in Claim 1 or Claims 5 to 8 and X is selected from Cl, Br or I.

26. A compound of Claim 25 which is selected from the group of:

2-Chloro-*N*-(1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;

2-Chloro-*N*-(3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Chloro-*N*-(2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Chloro-*N*-(1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Bromo-*N*-(1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Iodo-*N*-(1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Iodo-*N*-(3-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide;
2-Iodo-*N*-(2-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide; or
2-Iodo-*N*-(1-methyl-1,2,3,4-tetrahydro-cyclopenta[*b*]indol-5-ylmethyl)-acetamide.

27. A compound of the formula:

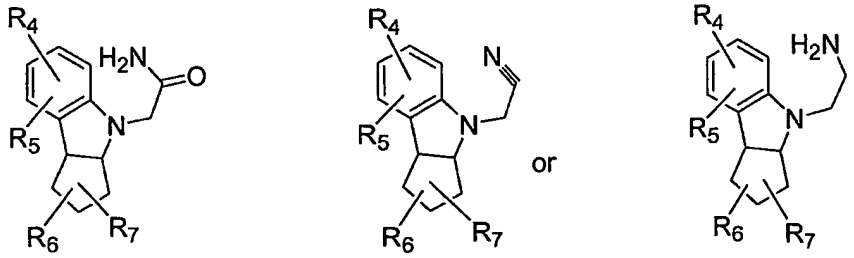


XXXV

wherein R_4, R_5, R_3, R_6 and R_7 are as defined in Claim 1 or claims 5-8.

28. A compound of Claim 27 which is one of the following:
4,5,9,10-Tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one;
8-Methyl-4,5,9,10-tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one;
9-Methyl-4,5,9,10-tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one; or
10-Methyl-4,5,9,10-tetrahydro-8*H*-5,7a-diaza-benzo[*cd*]cyclopenta[*a*]azulen-6-one.

29. A compound having one of the formulae:



wherein R_4, R_5, R_6 and R_7 are each, independently, hydrogen, hydroxy, alkyl of 1-6 carbon atoms, cycloalkyl, of 3 to 7 carbon atoms alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of from 1 to 6 carbon atoms, -CN, -NH-SO_2-alkyl of 1-6 carbon atoms, -SO_2-NH-alkyl of 1-6 carbon atoms, alkylamide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aryl, heteroaryl, aroyl or heteroaroyl.

30. A compound of Claim 29 wherein R_4 and R_5 are hydrogen, and R_6 and R_7 are as defined in Claim 1.

31. A compound of Claim 29 wherein R_4, R_5 and R_6 are hydrogen, and R_7 is as defined in Claim 1.

32. A compound of Claim 29 which is 2-(2,3,3a,8b-Tetrahydro-1H-cyclopenta[*b*]indol-4-yl)-acetamide.

33. A compound of Claim 29 which is one of the following:
2-(2,3,3a,8b-Tetrahydro-1*H*-cyclopenta[*b*]indol-4-yl)-acetamide;
2-(2,3,3a,8b-Tetrahydro-1*H*-cyclopenta[*b*]indol-4-yl)-acetonitrile, or
2-(2,3,3a,8b-Tetrahydro-1*H*-cyclopenta[*b*]indol-4-yl)-ethylamine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 May 2002 (30.05.2002)

PCT

(10) International Publication Number
WO 02/042304 A3

(51) International Patent Classification[7]: C07D 487/06, A61K 31/551, A61P 3/10

(21) International Application Number: PCT/US01/45792

(22) International Filing Date:
1 November 2001 (01.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/245,591	3 November 2000 (03.11.2000)	US
60/245,593	3 November 2000 (03.11.2000)	US
60/245,843	3 November 2000 (03.11.2000)	US
60/245,915	3 November 2000 (03.11.2000)	US
60/245,954	3 November 2000 (03.11.2000)	US

(71) Applicant: **WYETH** [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: **SABB, Annmarie, Louise**; 15 Meadow Lane, Pennington, NJ 08534 (US). **VOGEL, Robert, Lewis**; 20 Sleepy Hollow Road, Stratford, NJ 08084 (US). **NELSON, James, Albert**; 7 Decision Way West, Washington Crossing, PA 18977 (US). **ROSENZWEIG-LIPSON, Sharon, Joy**; 25 Bosko Drive, East Brunswick, NJ 08816 (US). **WELMAKER, Gregory, Scott**; 2 Jason Court, Jackson, NJ 08527 (US). **SABALSKI, Joan, Eileen**; 38 Elton Street, Yardville, NJ 08620 (US). **SMITH, Michael, David**; 315 Vista Way, Martinez, CA 94553 (US). **CHAN, Anita, Wai-Yin**; 1600 Center Avenue, Apartment 6D, Fort Lee, NJ 07024 (US). **ANTANE, Madelene, Miyoko**; 56 Lillie Street, West Windsor, NJ 08550 (US). **RAVEENDRANATH, Panolil**; 2 Whitman Place, Monroe, NY 10950 (US). **MEGATI, Sreenivasulu**; 1 Hearth Court, New City, NY 10956 (US).

(74) Agents: **ECK, Steven, R.**; WYETH, Patent Law Department, Five Giralda Farms, Madison, NJ 07940-0874 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

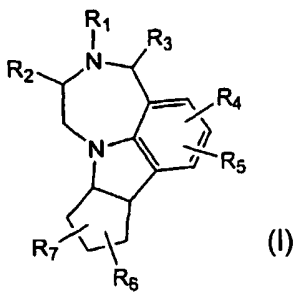
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

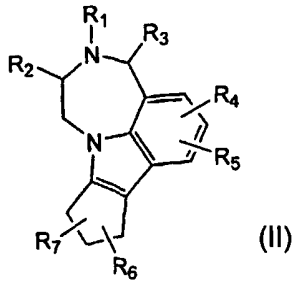
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

[Continued on next page]

(54) Title: CYCLOPENTA[B][1,4] DIAZEPINO[6,7,1-HI]INDOLES AS 5HT2C ANTAGONISTS



(I)



(II)

(57) Abstract: This invention provides compounds of the formulae: (I) or (II), wherein: R_1 is hydrogen, alkyl of 1-6 carbon atoms, atoms, acyl of 2-7 carbon atoms, aryl, heteroaryl, or -C(O)R' wherein R' is alkyl of from 1 to 6 carbon atoms, aryl, or heteoaryl; R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, alkoxy of 1-6 carbon atoms, $-CH_2OH$, fluoroalkyl, alkyl sulfonamide of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluoroalkyl, -CN, alkyl sulfonamide of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluoroalkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, or aroyl; R_6 and R_7 are each independently hydrogen, C_1-C_6 alkyl or cycloalkyl; or a pharmaceutically acceptable salt thereof, as well as pharmaceutical compositions containing these compounds and methods for their use, including treatment of obsessive-compulsive disorder, panic disorder, depression, anxiety, generalized anxiety disorder, schizophrenia, migraine, sleep disorders, eating disorders, obesity, epilepsy, and spinal cord injury.

WO 02/042304 A3

Published:
— *with international search report*

(88) Date of publication of the international search report:
29 August 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Int[illegible] onal Application No
PCT/US 01/45792

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/06 A61K31/551 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 08186 A (MERCK FROSST CANADA + CO., CAN.) 31 January 2002 (2002-01-31) page 21 -page 30; claim 1	1-33
A	US 3 914 250 A (KIM DONG H) 21 October 1975 (1975-10-21) cited in the application abstract; claim 1	1-33
A	WO 00 35922 A (AMERICAN HOME PROD) 22 June 2000 (2000-06-22) abstract	1-33
A	WO 96 29316 A (WIKSTROEM HAAKAN ;BOER PETER DE (NL); LIAO YI (NL)) 26 September 1996 (1996-09-26) abstract	1-33

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 June 2002	14/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[illegible]onal Application No
PCT/US 01/45792

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HESTERS J. B., ET AL.: "Pyrrolo'3,2,,1-jk!'1,4!benzodiazepines and Pyrrolo'1,2,3-ef!'1,5!benzodiazepines Which Have Central Nervous System Activity" J. MED. CHEM., vol. 13, no. 5, 1970, pages 827-835, XP002200700 cited in the application compounds 27-30 _____	1-33

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/US 01/45792

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0208186 6 A		NONE		
US 3914250 A	21-10-1975	NONE		
WO 0035922 A	22-06-2000	AU	3123400 A	03-07-2000
		BR	9916326 A	02-10-2001
		CN	1330652 T	09-01-2002
		CZ	20012193 A3	12-12-2001
		EP	1140940 A1	10-10-2001
		NO	20013001 A	15-06-2001
		SK	8192001 A3	03-12-2001
		WO	0035922 A1	22-06-2000
WO 9629316 A	26-09-1996	AU	5130596 A	08-10-1996
		WO	9629316 A1	26-09-1996